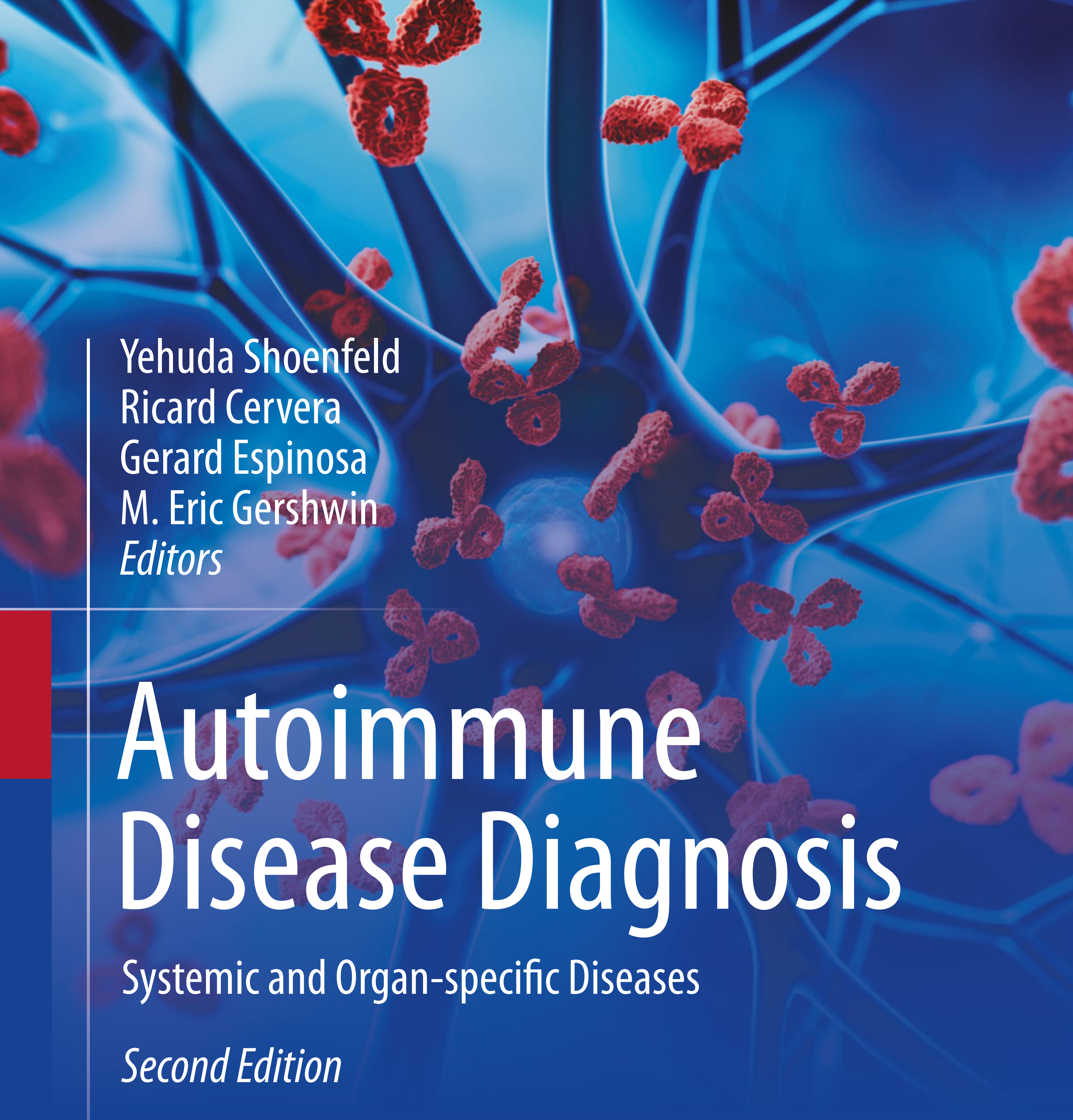

Yehuda Shoenfeld
Ricard Cervera
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Editors

Autoimmune Disease Diagnosis

Systemic and Organ-specific Diseases

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Foreword

The Challenges in Diagnosing Autoimmune Diseases

Autoimmune diseases do not adhere to clear-cut distinctions; rather, they fall into a medical realm characterized by different shades of complexity. Diagnoses are defined based on the clinical phenotype encompassing consistent patterns of manifestations, supported by laboratory, imaging, and/or histological findings. However, diagnostic uncertainty is a typically encountered phenomenon, especially in rheumatology. Importantly, autoimmune disorders often exhibit shared clinical symptoms and serological markers, rendering the differentiation among diseases challenging, especially during the early phases. Another factor contributing to this uncertainty is the heterogeneous nature of the diseases due to synchronous and non-synchronous involvement of multiple organs and a dynamic phenotype that evolves over time. *Vice versa*, various endotypes may emerge within the same autoimmune disease, possibly reflecting discrete underlying pathophysiological classes. This results in a prolonged period required to establish a more distinct presentation consistent with a specific disease. In fact, only a subset of clinical features, serological or other tests possess a sufficiently high level of diagnostic (or discriminating) accuracy. This is further complicated by the absence of a universally accepted *gold standard* for diagnosis across the majority of these conditions. As a result, the process of delineating these diseases becomes intricate, often demanding a holistic evaluation of clinical and laboratory data at consecutive time-points to reach a conclusive and accurate diagnosis [1, 2].

Diagnostic Delays and Their Impact on Disease and Patient Prognosis

Accruing evidence highlights the crucial role of early diagnosis and intervention in enhancing the prognosis of individuals with autoimmunity [3]. The extent of diagnostic delays observed across these diseases ranges between a few months to more than 5–10 years although there is tendency toward earlier recognition over the past decades [4–6]. This timeframe is influenced by a variety of factors including sociodemographic parameters, access to healthcare units and specialists, and the phenotype of each individual patient. The inherent uncertainty in diagnosis often compels physicians to postpone assigning a definitive disease label, particularly in cases where the manifestations do not pose an immediate threat to life. Nonetheless, difficult or long diagnostic journeys can cause persistent insecurity and anxiety, health-care avoidance, and symptom underreporting by patients [7].

Diseases characterized by gradual progression over time, lacking life-threatening manifestations, and exhibiting common, non-specific symptoms like low back pain, as seen in axial spondyloarthritis, can lead to diagnostic delays that extend beyond 8 years. Such patients tend to experience impaired quality of life and poorer outcomes in terms of disease activity, functional limitations, spinal mobility, and/or radiographic damage, as compared to counterparts with earlier diagnosis [8].

Conversely, disorders characterized by potentially organ- or life-threatening complications necessiate early diagnosis and prompt administration of appropriate treatment. This is exemplified in giant cell arteritis (GCA), where even modest diagnostic delays or treatment deferrals can result in irreversible vision loss [9]. Likewise, the importance of prompt identification, diagnosis, and management of small-vessel vasculitis affecting the lung or kidney parenchyma, or causing severe peripheral neuropathy, cannot be overemphasized. A diagnostic delay in systemic lupus erythematosus (SLE), an archetype systemic autoimmune disease with marked heterogeneity, has been linked to worsened patient-reported outcome measures (PROMs) such as compromised physical functioning, heightened disease activity, increased risk for flares and damage accrual, and poor kidney and central nervous system outcomes [6, 10–12]. In rheumatoid arthritis (RA), a diagnosis that is delayed beyond the span of 12 months is correlated with heightened radiological damage evident after a 5-year follow-up period [5]. Notably, the initial 12-week period from the onset of symptoms is recognized as a therapeutic "window of opportunity," wherein timely and targeted treatment interventions can yield improved clinical outcomes in patients with RA [13]. A similar concept has been introduced for SLE with the early use of hydroxychloroquine and prompt initiation of biological agents such as belimumab, due to their potential to modify disease trajectory and mitigate organ damage [14–16].

Diagnostic Versus Classification Criteria in Autoimmune Diseases

The relevance of developing disease (or diagnostic) criteria has been in the foreground for several decades [17]. The earliest sets of criteria were referred to as *diagnostic* and were formulated by experts without systematic data collection, analysis, or validation. These criteria outlined how diseases should be diagnosed; however, later on, it became apparent that they underperformed in accurately diagnosing individual cases. Consequently, disease *classification* criteria were gradually introduced, which are designed primarily for research purposes. Classification criteria serve as standardized definitions aimed at ensuring uniform cohorts for clinical research studies. In other words, these criteria aim to establish relatively homogeneous groups that can be effectively compared across diverse studies and geographical regions. Despite a compromise in sensitivity, classification criteria offer a notably high specificity.

It is important to emphasize that classification criteria are not meant to infer any treatment or insurance implications for patients. This contrasts the concept of diagnostic criteria which comprise a compilation of signs, symptoms, and assessments designed to guide clinical decision-making in routine patient care. Their purpose is to steer the disease management. These criteria need to encompass a wide spectrum of features, thus reflecting the inherent disease heterogeneity. A crucial objective is to achieve both high specificity and sensitivity, approaching the threshold of 100%, which is however an imposing goal. Particularly for autoimmune diseases, crafting diagnostic criteria represents a considerable, unmet challenge. The formulation of a singular, universally applicable set of diagnostic criteria is often viewed as unrealistic due to the divergent disease prevalence across distinct geographical regions and racial backgrounds. Based on these points, regulatory bodies such as the European Alliance of Associations for Rheumatology and the American College of Rheumatology no longer consider the funding or endorsement of diagnostic criteria [18].

Although diagnostic and classification criteria have different intended purposes, nonetheless in practice, the latter are commonly treated as compatible with the former [2]. To this end, there has been debate regarding the feasibility of employing classification criteria for diagnostic purposes under specific circumstances, prompting the question of whether classification criteria and diagnosis should be treated as distinct entities [19]. From a clinical standpoint, diagnosis is actually a form of disease classification. Also, the methodological approach used to develop either classification or diagnostic criteria is quite similar and includes experts nominating potential criteria elements, conducting an exhaustive literature review, scrutinizing medical records, appraising prevailing diagnostic methods, determining the sensitivity and specificity of prospective criteria elements, formulating and ranking candidate criteria elements, achieving consensus on the finalized criteria components, agreeing on criteria weights, and deciding whether to include entry criteria or not. Finally, setting as prerequisite the *diagnostic* criteria to possess nearly 100% sensitivity and 100% specificity deviates from the fact that the diagnostic reasoning process may be subject to human error. Conversely, it is crucial to emphasize that attaining a clinical diagnosis might demand supplementary information that falls outside the scope of the employed criteria [20]. The possibility of a diagnosis should not be ruled out solely based on the non-fulfillment of classification criteria, as these criteria often exhibit lower sensitivity for atypical or the early forms of autoimmune diseases [21],

SLE serves as an illustrative example for the evolutionary trajectory of autoimmune disease classification criteria over the past decades. The initial 1971 criteria for SLE classification underwent revisions, incorporating advances in immunologic knowledge to enhance disease classification. The 1982 revised criteria introduced serological markers such as fluorescence antinuclear antibody (ANA) and antibodies to DNA and Smith antigen. Initial studies in 1982 reported an impressive sensitivity and specificity of 96% [22]. However, ongoing research revealed that especially at early disease stages, the sensitivity was approximately 80%. In response, the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE were developed, prioritizing high sensitivity while maintaining modest specificity [23]. However, the limited specificity poses challenges for both research purposes and clinical applications since individuals with other autoimmune conditions such as scleroderma or Sjogren's syndrome might be misclassified as having SLE. An additional illustration of this issue is the 2017 McDonald criteria for multiple sclerosis diagnosis. These criteria, intended to enhance sensitivity for early identification and intervention, unfortunately resulted in high rates of misdiagnosis [24]. To address these limitations for SLE, a joint EULAR and ACR collaboration was established in 2019 seeking to devise improved classification criteria. This comprehensive initiative integrated a robust methodology that harmonized expert consensus with a data-driven approach. This process proceeded through several stages: criteria generation through systematic reviews, expert Delphi panels, international cohorts, and patient surveys; subsequent criteria reduction; definition and weighting of criteria; and the final refinement and validation. This comprehensive approach yielded a final set of criteria with the best combination of high sensitivity and specificity for SLE [25], suggesting that classification criteria might indeed provide the basis toward eventually developing diagnostic criteria.

In conclusion, the advancement of methodologies and possibly, integration of biomarkers create novel opportunities to construct accurate classification/diagnostic algorithms. To achieve this, we need to analyze extensive datasets encompassing diverse subsets of autoimmune cases, incorporating patients encountered in various clinical settings, such as primary care and internal medicine. Moreover, we need to acknowledge the impact of severe manifestations and consider features suggestive of common alternative diagnoses. The spectrum of "disease controls" should be expanded to encompass entities like infectious and malignant conditions. Innovative efforts aimed at formulating new diagnostic or classification criteria should prioritize a comprehensive analysis of the implications of misclassification. This involves assessing the effects on healthcare practitioners, the financial burden on the healthcare system, and the consequences for patients. It is imperative to scrutinize the impact on various facets of the autoimmune diseases, including disease outcomes and quality of life, in cases of both overdiagnosis and underdiagnosis. Importantly, to achieve the endeavor of developing diagnostic criteria, we will need to confront our fear of diagnostic uncertainty.

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Preface

There are over a dozen textbooks of physiology in use at medical schools, which provide meticulously detail on the complex workings of our tissues and organs. However, none of them includes significant information on the immune response. In contrast, virtually every textbook of medicine, which details and describes the innumerable human disease states, rarely includes a chapter that does not discuss human immunity. In fact, the immune system is the most promiscuous, far-reaching, and likely the oldest physiological system in the human body. We can retreat to the evolutionary history of the hagfish, potentially earlier, and to gain insight into the phylogeny and ontogeny of immune system development. Autoimmunity, the process by which our immune system turns on itself, is one aspect of immunopathology.

Autoimmune diseases are a family of more than 100 chronic, and often disabling, illnesses that develop when underlying defects in the immune system lead the body to attack its own organs, tissues, and cells. According to the Autoimmune Diseases Coordinating Committee (ADCC), they affect, collectively, between 14.7 and 23.5 million people in the USA—up to 8% of the population—and their prevalence is rising. Therapeutics have made life-saving advances, but for some diseases, patients face a lifetime of illness and treatment with debilitating symptoms, loss of organ function, reduced productivity at school and work, and high medical expenses. And, because most of these diseases disproportionately afflict women and are among the leading causes of death for young and middle-aged women, they impose a heavy burden on patients' families and on society. Our groups have advocated that research must be directed to reduce the impact of these conditions. These efforts should include, among other goals, the generation of more accurate epidemiologic profiles of autoimmune diseases, the development of a greater understanding of the fundamental biological principles underlying disease onset and progression, the provision of improved diagnostic tools to permit pre-clinical or pre-symptomatic diagnosis as well as newer metrics for diagnosis and monitoring, the creation of more effective interventions, and the production of public and professional education and training programs. Additionally, it is of paramount importance to develop biomarkers that can enable earlier diagnosis as well as aid physicians in selecting and monitoring treatment. New technologies, such as genomics, proteomics, and microbial analysis, may give the tools to study gene and protein patterns in tissue samples, providing vital insights into the onset and progression of disease. However, we also need to gain a better understanding of the distribution of these diseases through epidemiologic studies and of the environmental triggers that contribute to their onset. We must work to apply the knowledge provided by the Human Genome Project toward elucidating the hereditary risks of autoimmune diseases. As we learn more about the genetic and environmental factors contributing to these diseases, we will be able to develop effective prevention strategies that arrest the autoimmune process before it can irreversibly damage the body.

The first and most essential step in the management of autoimmune diseases is, no doubt, the recognition of the autoimmune disease itself by the attending physician. Autoimmune diseases can affect any part of the body and have a myriad of clinical manifestations that make diagnosis an extremely difficult task. At the same time, autoimmune diseases share many features both at their onset and during follow-up. Furthermore, the overlap of genetic traits can increase susceptibility to various autoimmune diseases, leading to a patient experiencing multiple autoimmune disorders or multiple autoimmune diseases occurring within the same family.

Conversely, despite the diversity in their presentation and natural history, autoimmune diseases share a number of underlying mechanisms and thus have the potential to respond to treatment with the same or related therapies. More selective and less toxic immunosuppressive and immunomodulatory agents are currently being used to treat these disorders, and promising immune tolerance approaches are emerging. However, several factors limit our ability to conduct the most efficient clinical trials. For example, we lack standardized classification and diagnostic criteria for many autoimmune diseases.

We believe that autoimmune diseases by and large have a genetic background (i.e., HLA DRB1, PTPN, etc.), which indicates subject with aggressive, beneficial immune system. This active immune system is advantageous in evolution, thus giving protection against infectious agents. Yet, this hyperactive immune system (especially present in women of child-bearing ages—explaining why 83% of all autoimmune diseases affect women) puts them at risk of developing autoimmune diseases once exposed to a hyper-stimulating environmental agate which overstimulates the immune system (i.e., EBV, COVID-19 virus, silicone implants, etc.).

These problems have prompted the editors of this volume to compile a comprehensive handbook, featuring a critical review of more than 120 autoimmune diseases, divided into 2 main groups, systemic and organ-specific autoimmune diseases. We aim to provide a contemporary overview of these conditions with special emphasis on diagnosis. Each chapter provides the essential information required by attending physicians as well as bench scientists to understand the definition, diagnostic criteria, and treatment of a specific autoimmune disease. Moreover, established classification and diagnostic criteria have been cited whenever available, and the authors have been requested to propose such criteria when none exists. The editors have produced a book of considerable intellectual caliber and this would not have been possbile without the enthusiastic support of the authors.

Finally, and most importantly, this text is dedicated to the individuals affected by autoimmune diseases, with the hope that one day they will find a cure.

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Contents

Part I Classical Systemic Autoimmune Diseases

1 Systemic Lupus Erythematosus . . . 3
Giuseppe Barilaro, Gerard Espinosa, and Ricard Cervera

2 Antiphospholipid Syndrome . . . 11
Giuseppe Barilaro, Gerard Espinosa, and Ricard Cervera

3 Rheumatoid Arthritis . . . 19
Virginia Ruiz-Esquide and José A. Gómez-Puerta

4 Juvenile Idiopathic Arthritis . . . 25
Eli M. Eisenstein and Yackov Berkun

5 Adult-Onset Still's Disease (AOSD) . . . 31
Maria Kourilovitch and Claudio Galarza-Maldonado

6 Systemic Sclerosis . . . 37
Gema Maria Lledó and Gerard Espinosa

7 Sjögren Disease . . . 47
Soledad Retamozo, Pilar Brito-Zerón, and Manuel Ramos-Casals

8 Mixed Connective Tissue Disease . . . 55
Giammarco De Mattia, Chiara Stagnaro, and Marta Mosca

9 Relapsing Polychondritis . . . 61
Philippe Mertz and Laurent Arnaud

10 Raynaud's Phenomenon (RP) . . . 67
Mario García-Carrasco, Mario Jiménez-Hernández, Ivet Etchegaray-Morales, and Pamela Munguía-Realpozo

11 Drug-Induced Autoimmunity . . . 75
Martine Szyper-Kravitz, Yehuda Shoenfeld, and Abihai Lucas Hernández

12 Polyautoimmunity and Multiple Autoimmune Syndromes . . . 81
Manuel Rojas, María Herrán, and Juan-Manuel Anaya

Part II Systemic Vasculitis

13 Giant Cell Arteritis . . . 91
Olga Araújo, Andrea Vendola, José Hernández-Rodríguez, and Sergio Prieto-González

14 Polymyalgia Rheumatica . . . 99
José Hernández-Rodríguez, Andrea Vendola, Sergio Prieto-González, Verónica Gómez-Caverzaschi, and Olga Araújo

15 Takayasu Arteritis 107
José Hernández-Rodríguez, Verónica Gómez-Caverzaschi, Antonio López-Rueda, Andrés González-García, and Curry L. Koening

16 Polyarteritis Nodosa 115
José Hernández-Rodríguez, Sergio Prieto-González, Verónica Gómez-Caverzaschi, Georgina Espígol-Frigolé, and Maria C. Cid

17 Microscopic Polyangiitis 123
Roberto Rios-Garcés, Adriana P. Garcia, Javier Marco-Hernández, Ariadna Hernández-Garcia, Marco Antonio Alba, and Georgina Espígol-Frigolé

18 Granulomatosis with Polyangiitis 131
Marco A. Alba, Oriol Llargués, Alba Jerez-Lienas, Andrea Núñez-Conde, Ignasi Rodríguez-Pintó, and Georgina Espígol-Frigolé

19 Eosinophilic Granulomatosis with Polyangiitis (EGPA, Churg–Strauss) 139
Yann Nguyen and Loïc Guillevin

20 Buerger's Disease 155
Yonatan Shneor Patt, Waseem H. Abu-Obeida, Abdulla Watad, and Michael Ehrenfeld

21 Behçet's Disease 161
Gerard Espinosa

22 Susac Syndrome 167
Manuel F. Ugarte-Gil and Gerard Espinosa

23 Anti-Glomerular Basement Membrane Disease (Goodpasture's Syndrome) 173
Miquel Blasco Pelicano and Luis F. Quintana

24 Kawasaki Disease 177
Jordi Antón

25 Cogan's Syndrome 183
Aharon Kessel, Zahava Vadasz, and Elias Toubi

26 Immunoglobulin A Vasculitis 187
Olga Araújo, Andrea Vendola, Verónica Gómez-Caverzaschi, and José Hernández-Rodríguez

27 Cryoglobulinemic Vasculitis 195
Andrés González-García, Ángel Robles-Marhuenda, Olga Araújo, Grisell Starita Fajardo, Verónica Gómez-Caverzaschi, and José Hernández-Rodríguez

28 Hypocomplementemic Urticarial Vasculitis (Anti-C1q Vasculitis) 203
Ángel Robles-Marhuenda, Olga Araújo, Verónica Gómez-Caverzaschi, Andrés González-García, and José Hernández-Rodríguez

29 Single-Organ Vasculitis 213
José Hernández-Rodríguez, Leonard H. Calabrese, and Gary S. Hoffman

Part III Idiopathic Inflammatory Myopathies

30 Polymyositis 225
Gema M. Lledó-Ibáñez, Jorge Álvarez Troncoso, and Sergio Prieto-González

31 Dermatomyositis 231
Claudio Cruciani, Margherita Zen, Anna Ghirardello, and Andrea Doria

32 Sporadic Inclusion Body Myositis 241
Albert Selva-O'Callaghan, Ana Matas-Garcia, and Jose Milisenda

33 Antisynthetase Syndrome 247
Jorge Álvarez Troncoso, Gema M. Lledó-Ibáñez, Estíbaliz Ruiz-Ortiz, Mariana Benegas, Fernanda Hernández, and Sergio Prieto-González

34 Immune-Mediated Necrotizing Myopathy 255
Wafa Elgeadi Saleh and Sergio Prieto-González

35 Granulomatous Myositis 261
Carlos Hernández Cerón, Pablo López Mato, Gema M. Lledó-Ibáñez, and Sergio Prieto-González

36 Eosinophilic Myositis 267
Albert Selva-O'Callaghan, Ernesto Trallero-Araguás, and Jose Milisenda

37 Eosinophilic Fasciitis 271
Albert Selva-O'Callaghan, Iago Pinal-Fernández, Ernesto Trallero-Araguás, and Albert Gil-Vila

Part IV Other Immune-Mediated Systemic Diseases

38 Sarcoidosis 279
Juan Mañá and Adriana Iriarte

39 Spondyloarthritis 287
Uria Shani, Abdulla Watad, and Michael Ehrenfeld

40 Familial Mediterranean Fever 295
Yackov Berkun and Eli M. Eisenstein

41 VEXAS Syndrome 301
José Hernández-Rodríguez, Verónica Gómez-Caverzaschi, Jordi Yagüe, Andrés González-García, Ángel Robles-Marhuenda, and Luca Cantarini

42 Fibromyalgia 309
Scott Ehrenberg, Adi Hertz, and Howard Amital

43 IgG4-Related Disease 317
Christopher Nguyen, José Hernández-Rodríguez, and Andreu Fernández-Codina

44 ASIA Syndrome 323
Vânia Borba, Abihai Lucas Hernández, Abdulla Watad, and Yehuda Shoenfeld

45 Immune Adverse Effects Induced by Checkpoint Inhibitors 329
Juan C. Sarmiento-Monroy and José A. Gómez-Puerta

Part V Endocrine and Reproductive Autoimmune Diseases

46 Hashimoto's Thyroiditis 339
Ifigenia Kostoglou-Athanassiou and Yehuda Shoenfeld

47 Atrophic Autoimmune Thyroiditis 345
Luis J. Jara, Gabriela Medina, María Pilar Cruz-Domínguez, Andrés Muñoz Solís, Olga Vera-Lastra, and Miguel Angel Saavedra

48 Subacute Thyroiditis . . . 351
Pamela Munguia Realpozo, Juan Jakez Ocampo, Socorro Méndez Martínez, and Mario García Carrasco

49 Graves' Disease . . . 355
Claudia Mendoza Pinto, José Luis Gálvez Romero, and Mario García Carrasco

50 Postpartum Thyroiditis . . . 361
Carlos Abud Mendoza, Edith Ramírez Lara, and Mario García Carrasco

51 Autoimmune Diabetes Mellitus . . . 367
Antonio Jesús Blanco-Carrasco

52 Autoimmune Adrenalitis . . . 375
Rodrigo Antonio Brandão Neto and Jozélio Freire de Carvalho

53 Autoimmune Hypophysitis . . . 381
Alberto Falorni, Michelantonio De Fano, Elena Bartoloni, Carlo Perricone, Giacomo Cafaro, and Roberto Gerli

54 Autoimmune Parathyroid Disease . . . 387
Corrado Betterle, Chiara Sabbadin, Jadwiga Furmaniak, and Fabio Presotto

55 Autoimmune Polyendocrine Syndromes . . . 395
Maurizio Cutolo and Emanuele Gotelli

56 Endometriosis . . . 401
María Angeles Martínez-Zamora and Francisco Carmona

57 Autoimmune Ovarian Insufficiency . . . 407
Aina Borrás and Francisco Carmona

58 Autoimmune Orchitis . . . 413
Clovis Artur Almeida da Silva, Marcello Cocuzza, Eduardo Ferreira Borba, Jozélio Freire de Carvalho, and Eloísa Bonfá

Part VI Hepatobiliary and Pancreatic Autoimmune Diseases

59 Autoimmune Hepatitis . . . 421
Maria-Carlota Londoño and Sergio Rodríguez-Tajes

60 Primary Biliary Cholangitis . . . 427
Patrick S. C. Leung, Tihong Shao, Li Wang, Koichi Tsuneyama, Pietro Invernizzi, Suraj Timilsina, and M. Eric Gershwin

61 Primary Sclerosing Cholangitis . . . 433
Ronald Hsu, Patrick S. C. Leung, Pietro Invernizzi, and M. Eric Gershwin

62 Autoimmune Pancreatitis . . . 441
Guillem Soy and Eva C. Vaquero

Part VII Gastrointestinal Autoimmune Diseases

63 Autoimmune Gastritis . . . 451
Leticia Moreira

64 Ulcerative Colitis . . . 459
Elena Ricart

65 Crohn's Disease . . . 465
Agnès Fernández-Clotet

66 Celiac Disease 471
Albert Martín-Cardona and Maria Esteve

Part VIII Cutaneous Autoimmune Diseases

67 Cutaneous Lupus Erythematosus 481
Annegret Kuhn

68 Pemphigus and Bullous Pemphigoid 489
Daniel Mimouni and Meital Oren-Shabtai

69 Vitiligo 495
Riad Kassem, Sharon Baum, and Aviv Barzilai

70 Psoriatic Arthropathy 501
Elias Toubi

71 Autoinmune Alopecia/Alopecia Areata 505
Andrea Combalia

72 Hidradenitis Suppurativa 509
Priscila Giavedoni and Irene Fuertes de Vega

73 Other Immune-Mediated Dermatosis (Lichen Planus, Erythema Multiforme, Toxic Epidermal Necrolysis, Graft-Versus-Host Reaction) 515
Xavier Bosch-Amate, Priscila Giavedoni, and Cristina Carrera

Part IX Cardiovascular and Pulmonary Autoimmune Diseases

74 Autoimmune Dilated Cardiomyopathy 525
Udi Nussinovitch, Yehuda Shoenfeld, and Abihai Lucas Hernández

75 Rheumatic Fever 531
Yaniv Sherer, Yehuda Shoenfeld, and Abihai Lucas Hernández

76 Accelerated Atherosclerosis in Autoimmune Diseases 535
Sara Monti, Pier Luigi Meroni, and Nicoletta Ronda

77 Idiopathic Interstitial Pneumonias 541
Eli Nancy Perez-Rodas, Jacobo Sellares, and Fernanda Hernandez-Gonzalez

78 Pulmonary Arterial Hypertension 549
Isabel Blanco and Joan Albert Barberà

Part X Neurological Autoimmune Diseases

79 Multiple Sclerosis 559
J. M. Cabrera-Maqueda and Y. Blanco

80 Myasthenia Gravis 567
Wakar Garra and Yair Levy

81 Paraneoplastic Neurological Syndromes 571
Francesc Graus

82 Guillain-Barre Syndrome and Other Immune-Mediated Neuropathies 577
Natalia Gavrilova, Evelina Kamaeva, Lidiia Soprun, Avraham Unterman, Yehuda Shoenfeld, and Joab Chapman

83 **Neuromyelitis Optica** 583
Natalia Gavrilova, Evelina Kamaeva, Lidiia Soprun, Yehuda Shoenfeld, and Joab Chapman

84 **Central Nervous System Vasculitis** 587
Gisele Zandman-Goddard, Ron Dabby, Alexander Puzhevsky, and Milena Tocut

85 **Autoimmune Chorea** 593
Natalia Gavrilova, Evelina Kamaeva, Lidiia Soprun, Ziv Paz, Yehuda Shoenfeld, and Joab Chapman

86 **Autoimmune Sensorineural Hearing Loss** 597
Aharon Kessel and Elias Toubi

87 **Autoimmune Encephalitis** 603
Mar Guasp and Josep Dalmau

88 **Autoimmune Dysautonomia** 611
Judith Navarro-Otano

89 **Cerebellar Autoimmune Diseases** 615
Maria Sepúlveda and Francesc Graus

90 **Autoimmune Disturbances of Sleeping** 621
Carles Gaig and Amaia Muñoz-Lopetegi

91 **Autoimmune Stiff-Person Syndromes** 629
Sara Llufriu

Part XI Ocular Autoimmune Diseases

92 **Autoimmune Retinopathies** 635
Alfredo Adán

93 **Autoimmune Uveitis** 639
Alfredo Adán

94 **Vogt-Koyanagi-Harada Disease** 643
Felipe Freire da Silva, Joyce Hisae Yamamoto, and Jozélio Freire de Carvalho

95 **Orbital Myositis** 649
Carlos Hernández Cerón, Pablo López Mato, Jèssica Matas, and Sergio Prieto-González

Part XII Renal Autoimmune Diseases

96 **IgA Nephropathy** 655
Jordi Ara

97 **Membranous Nephropathy** 663
Marc Xipell and Luis F. Quintana

98 **Minimal Change Disease** 669
Marc Xipell and Luis F. Quintana

99 **Focal and Segmental Glomerulosclerosis** 673
Montserrat Diaz-Encarnación, Anna Dominguez, Yolanda Arce, Xoana Barros, and Helena Marco

100 Membranoproliferative Glomerulonephritis 681
Montserrat Diaz-Encarnación, Gerson Berna, Yolanda Arce, Xoana Barros, and Helena Marco

101 Acute Tubulointerstitial Nephritis 687
Marc Xipell and Luis F. Quintana

102 Atypical Hemolytic Uremic Syndrome 691
Miquel Blasco Pelicano

Part XIII Hematologic Autoimmune Diseases

103 Autoimmune Hemolytic Anemia 699
Meritxell Nomdedeu, Joan Cid, Gabriela Simona Ene, Alexandra Pedraza, Arturo Pereira, and Cristina Sanz

104 Pernicious Anemia 705
Mario García-Carrasco, Mario Jiménez-Hernández, Adriana Rojas-Villarraga, and Guillermo J. Ruiz-Argüelles

105 Idiopathic Aplastic Anemia 711
Baraf Lior, Levy Yair, Yehuda Shoenfeld, Gabriela Roque González, and Abihai Lucas Hernández

106 Acquired Adult Pure Red Cell Aplasia 717
Hedi Orbach, Gisele Zandman Goddard, Asher Winder, Yehuda Shoenfeld, and Abihai Lucas Hernández

107 Autoimmune Neutropenia 723
Amani Mankaï, Sophie Hillion, Yehuda Shoenfeld, Christian Berthou, Ibtissem Ghedira, and Abihai Lucas Hernández

108 Immune Thrombocytopenia 727
Yulia Einav, Nurit Rosenberg, Boris Shenkman, Yehuda Shoenfeld, Rocio Moran Contla, and Abihai Lucas Hernández

109 Thrombotic Thrombocytopenic Purpura and Other Thrombotic Microangiopathic Hemolytic Anemias 733
Boris Shenkman, Yulia Einav, Ophira Salomon, Yehuda Shoenfeld, Rocio Morán Contla, and Abihai Lucas Hernández

110 Heparin-Induced Thrombocytopenia 741
Joan Carles Reverter and Dolors Tàssies

111 Autoimmune Coagulopathies 747
Dolors Tàssies and Joan Carles Reverter

Index 753

Part I

Classical Systemic Autoimmune Diseases

1 Systemic Lupus Erythematosus

Giuseppe Barilaro, Gerard Espinosa, and Ricard Cervera

Abstract

Systemic lupus erythematosus (SLE) represents the paradigm of systemic autoimmune disease, characterized by a wide range of clinical manifestations and the production of multiple autoantibodies. The diagnosis is based on the clinical features along with the presence of a wide variety of autoantibodies, most of which are directed against double-stranded DNA (ds-DNA), nuclear antigens, ribonucleoproteins, and cell surface antigens. The treatment relies on antimalarials, corticosteroids, conventional immunosuppressors, and new biological agents.

Keywords

SLE · dsDNA · SLEDAI · BILAG · Lupus nephritis · Belimumab · Anifrolumab

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease of unknown etiology, characterized by the production of autoantibodies directed toward several self-antigens found in the nucleus, cytoplasm, and cell surface and protean clinical manifestations. The primary pathological findings are inflammatory infiltrates, immune complex deposition, vasculitis, and vasculopathy. The clinical picture is typically characterized by periods of flares and remission.

SLE is one of the most common systemic autoimmune disorders, primarily affecting young women (with an average female-to-male ratio of 9:1), although any age could be affected, from the neonatal period to the elderly. Black, Hispanic, and Asian populations are disproportionately affected in comparison to white Caucasians. Male patients seem to have a more severe disease, as black populations compared to other races.

ANA positivity is the laboratory hallmark of the disease, being present in more than 95% of patients, and it is mandatory to classify a patient as having SLE as per new classification criteria [1]. Typical antinuclear antibodies (ANA) pattern is diffuse/homogeneous staining. Specific SLE antibodies are anti-double-stranded DNA (dsDNA) and anti-Sm antibodies, which are rarely found in other conditions. While anti-dsDNA titers frequently change in the course of disease and are a marker of disease activity, anti-Sm titers are usually constant.

SLE represents the prototype of systemic autoimmune disease, and any organ and system can be affected. Most common manifestations are oral ulcers, polyarthritis, and skin rashes. Exposure to the sun typically exacerbates clinical, especially cutaneous, manifestations. Kidneys and neuropsychiatric involvement are present in almost half cases, while hematologic manifestations, such as hemolytic anemia, leucopenia, and thrombocytopenia, are also frequent. Nonspecific features such as fatigue, fever, or anorexia are early common features of SLE.

SLE is one of the leading causes of death in young women, and, despite improvements in overall management and new treatment options that led to a better long-term prognosis, mortality in SLE patients is still high, with a standardized mortality ratio (SMR) two to three times higher than the general population [2].

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Genetics and Epidemiology

A strong genetic link has been identified in SLE through the application of family and large-scale genome-wide association studies (GWAS). Familial aggregation of SLE is well described and there is a high concordance rate between homozygotic twins. Genes implicated in clearing apoptotic debris, such as DR2 and DR3, ITGAM, PDCD1, TREX1, affecting the complement cascade (CR2, CR5, CFB), in intracellular signaling in B (CD40, BANK1, BLK, LYN) and T (CD44, CTLA-4, PTPN 22, TRAF1) cells and in the interferon pathway (IRF, IRAK1, STAT4, TRAF6), are the most studied.

Reports of the global incidence and prevalence of SLE vary widely, owing to inherent variation in population demographics (age, gender, race, and ethnicity), environmental exposures, and socioeconomic factors. Epidemiological studies have been conducted mainly in North America and Europe, most recent ones showing an incidence that goes from 3.7 to 49 per 100,000 population-years [3, 4] in the USA to 3.3 per 100,000 population-years in France [5] and 7.4 per 100,000 population-years in Crete (Greece) [6]. In South America, reported incidence rates vary between 1.4 and 6.3 per 100,000 population-years, while in Asia from 2.5 to 8.6 per 100,000 population-years [7]. The prevalence of SLE varies between 48 and 366.6 per 100,000 in North America, 29.3 and 210 in Europe, 24.3 and 126.3 in South America, and 20.6 and 103 in Asia [7]. Very little is known about the incidence of SLE in Africa and Australasia.

The presentation and course of the disease appear highly variable between patients of different ethnic origins, where African-Americans and Orientals are believed to have a more severe disease than Caucasian whites [8].

It is now known that anti-dsDNA antibodies may be present on average 2.7 years prior to diagnosis and up to 9.3 years earlier. Antinuclear antibodies (ANA) may occur earlier than anti-dsDNA antibodies. Interestingly, anti-Sm and anti-RNP antibodies appear shortly before diagnosis suggesting a crescendo of autoimmunity resulting in clinical illness [9].

Clinical Manifestations

Joints and muscles are the most frequently involved structures in SLE. Polyarthralgia, almost invariably symmetric and episodic, occurs in about 90% of SLE patients, being the initial symptom in about 50%. Non-deforming non-erosive arthritis is the most common form of arthritis, it can affect all major and minor joints, but the far most frequent presentation is symmetric proximal interphalangeal, metacarpal-phalangeal, and wrist involvement. Jaccoud's arthropathy, a non-erosive condition characterized by reversible joint deformities, is seen in about 10% of patients, as a result of chronic tenosynovitis that may lead to "swan-neck" deformities and ulnar deviation/subluxation. Generalized myalgia and muscle tenderness is observed in 40–80% of cases, but inflammatory myopathy, usually involving proximal muscles, is quite rare, not reaching 10%. Myopathy can also be caused by antimalarial and corticosteroid therapy.

The skin is a common target for the disease and cutaneous lesions occur in up to 85% of SLE patients, being the butterfly "Lupus" rash the most characteristic feature. This is an erythematous, often blotchy rash found mainly over malar bones and across nose bridge, typically sparing the nasolabial folds. Besides maculopapular and discoid-specific lesions of SLE, other non-specific lesions such as splinter hemorrhages, dilated capillaries at the nail base, bullous lesions, angioneurotic edema, and livedo reticularis can occur. Vasculitic skin lesions are usually found at the fingertips or on the extensor surface of the forearm, as well as in the malleoli, leading to tender, deep leg ulcers which can be difficult to treat.

The kidneys are frequently involved in patients with SLE. More than 70% of patients with SLE have renal involvement at some stage of their disease. The International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) updated the classification of lupus nephritis in 2018 including the National Institute of Health (NIH) modified lupus nephritis activity and chronicity scoring system to better define the degree of activity found in a renal biopsy [10]. Among the different pathological classes of lupus nephritis, class IV has the worst prognosis, with a 19% risk of end-stage renal disease at 5 years in developed countries [11].

Pleuritis (with or without pleural effusion) is the most frequent respiratory manifestation of SLE affecting 30–50% of SLE patients during the course of their disease. The effusions are normally small to moderate in size and are usually exudates. A pleural fluid ANA titer of at least 1:160 has a sensitivity of 92% for SLE pleuritis.

Parenchymal involvement has been described in up to 20% of patients, in the form of acute pneumonitis, chronic interstitial pneumonitis, and pulmonary vasculitis. Alternative etiologies, such as pulmonary infections, congestive heart failure, renal failure, drug-induced lung toxicity, and other autoimmune diseases and malignancies, must always be ruled out. Shrinking lung syndrome, a restrictive pattern with elevation of hemidiaphragms, clinically characterized by exertional dyspnea and pleuritic chest pain, presents in less than 1% of patients. Diffuse alveolar hemorrhage is rare but life-threatening and should prompt the search for antiphospholipid antibodies.

The clinical picture is characterized by dyspnea, pleuritic chest pain, and cough. Hemoptysis should raise the suspicion of alveolar hemorrhage. Pulmonary function tests determine the grade of extension and progression of this condition. Usually, they reveal a restrictive pattern, a reduction in the diffusing capacity for carbon monoxide (DLCO). Biopsies are non-specific, but some features such as mononuclear interstitial infiltrates and immunoglobulin and complement deposition may help in the diagnosis.

The heart can also be targeted in SLE, with acute pericardial effusion as the most common manifestation. Adhesive chronic pericarditis and very large effusions causing tamponade are very rare. While true myocardial involvement is less frequent than pericardial disease, prolongation of the PR interval (approximately 10%), fibrinoid degeneration, myocardial infarction, and coronary stenosis due to arteritis are occasionally seen. Systolic murmurs may reflect the hyperdynamic circulation due to anemia.

Libman-Sacks endocarditis is a rare but characteristic feature of SLE, which rarely causes clinically significant lesions. Cardiac valvular sterile vegetations are most frequently observed adjacent to the edges of mitral and tricuspid valves. Infectious endocarditis must always be excluded.

Neuropsychiatric involvement has been described in 10–90% of patients, usually occurring within the first years of diagnosis. The spectrum of CNS manifestations varies widely, from severe life-threatening presentations, such as transverse myelitis or stroke, to more subtle and subclinical abnormalities in neurocognitive functions, such as memory, intellect, and learning. Central nervous system (CNS) is far more affected than peripheral nervous system (PNS). The difficulty to attribute neuropsychiatric symptoms to SLE, the clinical diversity of the disorder, the difficulty to define outcome measures, and the lack of diagnostic criteria represent the biggest obstacles to study treatment options and compare different therapeutic regimens, which was partially improved after the introduction of 1999, by the ACR, of specific criteria for neuropsychiatric SLE (NPSLE). This nomenclature includes case definitions, reporting standards, and diagnostic testing recommendations for 19 neuropsychiatric syndromes: 12 CNS-related and 7 PNS-related.

Some of these manifestations, like cerebrovascular disease, movement disorders, seizures, transverse myelopathy, demyelination, cognitive dysfunction, visual loss, and headache, are clearly linked to antiphospholipid antibodies (aPL). A differential diagnosis with other conditions, such as multiple sclerosis, is difficult and electroencephalography may offer some clues suggestive of cerebrovascular insufficiency.

Oral ulcers are the most common gastrointestinal manifestation, occurring in up to 52% of patients. They are typically superficial, self-limiting, and painless. Conversely, discoid oral lesions may be severely painful. Abdominal pain is found in 8–37% and might be due to peritonitis, pseudo-obstruction, pancreatitis, enteritis, vasculitis, or ischemia with/without intestinal perforation.

Table 1.1 Signs and symptoms

Signs and symptoms	Range of %
Malar rash	35–57
Discoid rash	11–19
Non-scarring alopecia	36–62
Oral ulcers	18–38
Non-erosive arthritis	52–64
Serositis	18–23
Renal involvement	43–50
Neuropsychiatric manifestations	9–21
Hematologic disorders	77–86
Hemolytic anemia	18–30
Leucopenia	52–67
Thrombocytopenia	5–34

Hematologic manifestations include autoimmune hemolytic anemia, detected by Coomb's test, thrombocytopenia, that can be associated to the former configuring the so-called Evan's syndrome, and leucopenia (usually related to lymphopenia). Macrophage activation syndrome should be considered if cytopenia develops rapidly. Both hemolytic anemia and thrombocytopenia are associated with the presence of aPL. Lymphadenopathy may be dramatic in SLE, to such an extent that lymph node biopsy may have to be performed to exclude malignancy.

Other non-specific manifestations such as fever, hair loss, and Raynaud's phenomenon are all commonly found in SLE patients. Fever in lupus patients may be striking and often requires extensive investigation to exclude concurrent infection. Nevertheless, it discriminates so well between SLE and mimickers that it became the only entirely new item in the new European Alliance of Associations for Rheumatology (EULAR)/ACR criteria [1].

Table 1.1 reports the rate of main signs and symptoms in SLE as reported in a recent cross-sectional study with an associated meta-analysis [12].

Immunologic Markers

ANA testing is the first step in case of suspicion of SLE, being positive in almost all patients, and has been set as entry criterion in the new classification criteria. However, ANA positivity can be detected in a multitude of other conditions, such as infections, organ-specific and systemic autoimmune diseases, and also in healthy individuals, especially in old age. ANA positivity may anticipate the diagnosis of SLE in some cases. The gold standard for ANA testing is indirect immunofluorescence (IIF) on HEp-2 cells. However, since this technique is not available in all laboratories, other techniques, such as IIF on rodent tissues (kidney and liver) and

ELISA testing, are widely used and accepted. The typical SLE pattern is homogeneous, which is commonly produced by anti-histone antibodies while anti-RNP, anti-Sm, anti-Ro, and anti-La antibodies can produce a nuclear speckled pattern. Anti-dsDNA antibodies can give a rim and peripheral pattern and anti-ribosomal P antibodies have a cytoplasmic pattern.

Anti-dsDNA antibodies are specific for SLE, being present in 60–80% of cases. They are tested by IIF on Chritidia Luciliae or ELISA assays. There is a strong correlation between anti-dsDNA levels and disease activity and their increase can precede a disease flare, particularly of renal disease. Anti-Sm antibodies are also specific, but their titers almost do not change over time and therefore monitoring their levels is of no value in clinical practice. Antinucleosome antibodies are reported in 60–80% of patients with SLE. They have also been found in some patients who were negative for anti-dsDNA, and in such cases can be used to confirm diagnosis.

Anti-Ro (SS-A) and anti-La (SS-B) antibodies are associated with neonatal lupus, a condition that involves newborns from mother with this antibodies positivity and is characterized by dermatologic manifestations usually in the form of subacute cutaneous lupus and, in about 2% of cases, by congenital heart block (CHB). The probability of CHB increases by 10–15 times in a subsequent pregnancy after a first episode. Anti-60 kDa Ro antibodies have been reported to be in close association with leucopenia, thrombocytopenia, interstitial pneumonitis, and vasculitis.

Anti-C1q antibodies have shown a strong correlation with lupus nephritis in several studies and their titers can be used as predictors of disease flares. However, their routine testing is not performed in most centers. Anti-histone antibodies have been shown to be associated with both SLE and drug-induced lupus.

Anti-ribosomal P antibodies have been associated by several authors to the onset of neuropsychiatric lupus, however this association seems controversial.

aPL can be found in about one-third of lupus patients and one-third of them present clinical manifestations of antiphospholipid syndrome, namely vascular thrombosis, and pregnancy morbidity. This aspect will be discussed in detail in the next chapter.

Table 1.2 reports the rate of immunological markers in SLE as reported in a large multicenter cross-sectional study [13].

Table 1.2 Immunologic markers

Marker	%
ANA	99
Anti-dsDNA	62.9
Anti-Ro (SSA)	40.1
Anti-La (SSB)	18
Sm	13.1
RNP	18.4
aCL/aß2GPI	37.3
LA	20.8
Low C3	53.5
Low C4	51.3
Hypergammaglobulinemia	32.7

Rate of immunologic markers. (Modified from Govoni et al. [13])
aß2GPI: anti-ß2-glycoprotein I antibodies; aCL: anticardiolipin antibodies; ANA: antinuclear antibodies; dsDNA: double-stranded DNA; RNP: anti-ribonucleoprotein; Sm: Smith

Diagnosis of SLE

Diagnosis of SLE hinges on a thorough assessment of clinical manifestations, laboratory features, and autoantibodies. The disease course follows a relapsing-remitting pattern in almost two-thirds of patients, in which symptoms occur intermittently and cumulatively over many years [14]. Nonspecific features, such as Raynaud's phenomenon, photosensitive rashes, fatigue, fever, and lymphadenopathies may suggest the diagnosis when specific manifestations are not present.

The first modern set of classification criteria was published in 1982 by the American College of Rheumatology (ACR), which was updated in 1997 including antiphospholipid antibodies [15]. With the aim of increasing sensitivity, a new set of classification criteria was devised in 2012 by the Systemic Lupus International Collaborating Clinics (SLICC), which separated clinical and immunological domain [16]. However, these new criteria had a lower specificity. For this reason, new classification criteria jointly supported by the EULAR and the ACR were embarked upon and led to the development of the new classification criteria in 2019. These criteria include ANA positivity ≥1:80 as an entry criterion plus weighted items split into clinical and immunological domains [1] (Table 1.3).

The EULAR/ACR criteria were tested in an independent validation split cohort of 696 SLE and 574 non-SLE patients showing a sensitivity of 96.1% similar to the SLICC criteria (96.7%) and higher than the ACR 1997 criteria (82.8%) and

Table 1.3 EULAR/ACR SLE classification criteria

Entry criterion ANA at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)			
If absent, do not classify as SLE If present, apply additive criteria			
Additive criteria Do not count a criterion if there is a more likely explanation than SLE Occurrence of a criterion on at least one occasion is sufficient Criteria do not need to occur simultaneously Within each domain, only the highest weighted criterion is counted toward the total scores			
Clinical domains and criteria	**Weight**	**Immunology domains and criteria**	**Weight**
Constitutional		**SLE-specific antibodies**	
Fever	2	Anti-dsDNA antibody Anti-Sm	6
Hematologic		**Complement proteins**	
Leucopenia	3	Low C3 OR low C4	3
Thrombocytopenia	4	Low C3 AND low C4	4
Autoimmune hemolysis	4		
Neuropsychiatric		**Antiphospholipid antibodies**	
Delirium	2	Anti-cardiolipin antibodies OR	2
Psychosis	3	Anti-ß2glycoprotein I antibodies OR	
Seizure	5	Lupus anticoagulant	
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5 g/24 h	4		
Renal biopsy Class I or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		
SLE classification requires at least one clinical criterion and ≥10 points			

a specificity of 93.4%, equal to the ACR criteria (93.4%) and higher than the SLICC criteria (83.7%), thus meeting their initial goals in both directions [1]. Another study tested their ability of predicting the disease, with a positive predictive value (PPV) of 88.5% and a negative predictive value (NPV) of 92.3% [17].

As with all classification criteria, SLE criteria are intended for research purposes, with the aim of homogenizing patients' populations for clinical studies. While not legitimately used for diagnostic purposes, they can serve as the basis for clinical decision-making in a disease such as SLE that lacks diagnostic criteria.

Disease Activity and Damage

Due to the heterogeneity of SLE, the assessment of disease activity and its differentiation from permanent damage represents a challenge. No biomarker reflects disease activity uniformly, and anti-dsDNA antibodies, complement levels, and markers of inflammation such as erythrocyte sedimentation rate or C-reactive protein are not always abnormal in active disease. Conversely, damage might also be a consequence of therapy side effects.

The objective assessment of lupus relies on a number of disease activity scoring systems. While the Systemic Lupus

Erythematous Disease Activity Index-2K (SLEDAI-2K), the Systemic Lupus Activity Measures (SLAM) and the SLE disease activity score (SLE-DAS) imply a rather “black and white” view of activity (an item scores if present, regardless of its severity), the British Isles Lupus Group (BILAG) uses the principle of the “physician’s intention to treat” distinguishing patients based on the level of treatment they need to control manifestations and gives a better “all round” capture of lupus activity features.

The SLICC/ACR Damage Index (SDI) is the only instrument available to measure damage. It was not designed to identify the precise cause of any item of damage, not least because this can be multiple and/or hard to ascertain. Identifying damage early in the course of the disease is of critical importance since it strongly predicts mortality.

Therapy and Prevention

Since SLE is a multisystem disease, it requires multidisciplinary management, with a shared decision-making process involving different professionals. Disease activity and damage should be assessed periodically using the above-described tools. Non-pharmacological interventions, such as sun protection, smoking cessation, and regular exercise, are crucial for good long-term outcomes.

Due to the wide range of severity in clinical manifestations, treatment varies depending on the organ involved and the extent of involvement. In general, the aim of treatment is to reach remission, as per the recent Definition Of Remission In SLE (DORIS) criteria [18], which consists of a clinical SLEDAI-2K = 0, a physician global assessment ≤0.5 while on hydroxychloroquine, a prednisone dose ≤5 mg and a stable immunosuppressive/biological therapy. When this target is not reachable, low disease activity as defined by the lupus low disease activity state (LLDAS), which includes a SLEDAI-2K ≤4, a physician global assessment ≤1 while on a predniso(lo)ne dose ≤7.5 mg with a stable immunosuppressive/biological therapy, has shown to correlate with better outcomes.

The EULAR has recently updated its SLE treatment guidelines, which made some substantial changes compared to the former [19]. Hydroxychloroquine (HCQ) represents the mainstay of treatment in SLE, and it is recommended in all patients with lupus, ideally at a dose not exceeding 5 mg/kg real body weight to reduce the risk of retinal toxicity. However, the last recommendations pointed out that the doses should be individualized based on risk for flare and retinal toxicity, with patients at higher risk for retinal toxicity (kidney disease, preexisting macular or retinal disease, tamoxifen use) being candidates for closer ophthalmologic follow-up. Quinacrine might be considered in patients with cutaneous manifestations and HCQ-induced retinopathy. Glucocorticoids dose depends on the type and severity of organ involvement. High-dose intravenous methylprednisolone (MP, usually 125–1000 mg/day for 3 days) is often used in acute, organ-threatening disease (e.g., renal, neuropsychiatric). However, the medium to long-term aim should be to minimize the daily dose to ≤5 mg/day prednisone or equivalent and, when possible, to withdraw it, to avoid treatment-related damage.

Conventional immunosuppressors, such as methotrexate (15–25 mg/week), azathioprine (2 mg/kg/day), and mycophenolate-mofetil (2–3 g/day) or mycophenolic acid (1440–2160 mg/day), are usually indicated as chronic therapy to reduce the dose of glucocorticoids. Biological therapies, namely belimumab (directed against B-cells activating factor) or anifrolumab (that inhibits the IFN-I receptor), should be considered in patients with persistent disease activity despite proper treatment, and inability to taper glucocorticoids to a safe daily dose (prednisone ≤5 mg). Moreover, the last recommendations pointed out that biological agents can be started also in patients immunosuppressors-naïve.

Mycophenolate mofetil (2–3 g/day) or cyclophosphamide (500 mg fortnightly for 6 infusions as per EUROLUPUS protocol) are the first line of treatment, in association with glucocorticoids (pulses of intravenous MP for 1–3 days followed by 0.3–0.5 mg/kg/day of oral prednisone), for class III/IV/V lupus nephritis. The association with belimumab (preferably in patients with a 24 h proteinuria below 3 g/day), tacrolimus, or voclosporin (a recently approved new calcineurin inhibitor that does not need hematological concentrations monitoring) should be considered in patients with inadequate response by 3–6 months (≥25–50% reduction in proteinuria).

Rituximab is a second-line therapy, in patients with life-threatening disease refractory to other treatments, although it might be used as first-line in case of cytopenias. Anti-CD19 chimeric antigen receptor T cell (CAR-T) therapy, in which T cells are modified by genetic engineering to acquire the ability to target a specific antigen, has been used in severe cases refractory to other treatments [20]. Daratumumab, a human monoclonal antibody that targets CD38, depletes plasma cells, and is approved for the treatment of multiple myeloma, has also been used with success in patients with life-threatening manifestations.

Conclusions

SLE is the most diverse of the autoimmune diseases, characterized by a wide range of clinical features and the production of multiple autoantibodies. The diagnosis is based on the clinical features and the presence of a wide variety of autoantibodies. A thorough assessment of the presenting clinical features, examination of all the organ systems, and routine blood and urine analysis are mandatory. Although the new EULAR/ACR classification criteria improved the former in terms of accuracy, these are specifically designed for research studies and should not be used for diagnosing the disease.

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2

Antiphospholipid Syndrome

Giuseppe Barilaro, Gerard Espinosa, and Ricard Cervera

Abstract

Antiphospholipid syndrome (APS) is the most common acquired thrombophilia and is characterized by the occurrence of arterial, venous, and/or microvascular thromboses and pregnancy morbidity, frequently accompanied by hematologic alteration, such as thrombocytopenia and hemolytic anemia, in the presence of antiphospholipid antibodies (aPL). Some estimates indicate that the incidence of APS is around 1–2 new cases per 100,000 persons per year and the prevalence is around 6–50 cases per 100,000 persons. APS is diagnosed in 10–15% of patients with systemic lupus erythematosus, 9.5% of patients with deep vein thrombosis, 17% of patients with stroke younger than 50 years old, and 6% of patients with pregnancy morbidity.

The original classification criteria for the APS were formulated at a workshop in Sapporo, Japan, in 1998, during the 8th International Congress on aPL and revised during another workshop in Sydney, Australia, in 2004, at the 11th International Congress on aPL. At least one clinical (vascular thrombosis or pregnancy morbidity) and one laboratory (presence of anticardiolipin IgG and/or IgM, anti-β2-glycoprotein I IgG and/or IgM, or lupus anticoagulant in at least 2 occasions at least 12 weeks apart) criterion had to be met for the classification of APS. Over the past decade, substantial evidence has accumulated on different clinical and laboratory aspects of APS, leading to the development of the new APS classification criteria, endorsed by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR), in 2023.

Keywords

Antiphospholipid syndrome · Anticardiolipin antibodies · Anti-β2-glycoprotein I · Lupus anticoagulant · Catastrophic antiphospholipid syndrome

Antiphospholipid syndrome (APS) is a hypercoagulability condition of autoimmune origin clinically characterized by the development of arterial, venous, and/or microvascular thrombosis, pregnancy complications (recurrent early miscarriages, fetal deaths after the tenth week of gestation and/or premature births), and, frequently, hematologic alterations (such as hemolytic anemia and thrombocytopenia), associated with the presence of antiphospholipid antibodies (aPL).

APS can occur either as an isolated condition (primary APS), or in the context of an underlying autoimmune disease, most commonly systemic lupus erythematosus (SLE). Less frequently, it can be associated with other autoimmune disorders, infections, drugs, and malignancies.

aPL are antibodies that bind to negatively charged phospholipids directly or via proteins, such as β2-glycoprotein I (β2GPI), that act as cofactors. Three aPL are included in the current classification criteria, anticardiolipin antibodies (aCL), aβ2GPI antibodies, and lupus anticoagulant (LA), but there are much more identified, that can be especially useful in case of high clinical suspicion not supported by concomitant aPL positivity, the so-called “seronegative” APS [1].

In a small subset of patients (about 1%), thrombosis can involve simultaneously (over days to weeks) multiple organs, configuring the so-called catastrophic APS (CAPS), which represents a life-threatening condition, whose prognosis improved dramatically after the introduction of the so-called triple therapy.

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Epidemiology

The aPL are not specific of APS and can be detected in healthy individuals, with an estimated prevalence of 0.1–5% [2]. The few estimates available rate the incidence of APS on a range from 0.75 to 2.1 per 100,000 population-year and the prevalence on a range from 6.2 to 50 cases per 100,000 population [3, 4]. There seems to be a female predominance with a female-to-male ratio around 3 to 5:1, but one population-based study reported a similar prevalence in both sexes [3]. The mean age of onset is between the fourth and the sixth decade even though childhood and older onsets have been described.

The prevalence of aPL has been estimated at about 11% among patients with myocardial infarction, 9.5% of patients with deep vein thrombosis, and 17% among patients with stroke younger than 50 years of age [5]. Moreover, aPL are positive in around 6% of women with pregnancy morbidity, representing the most frequent acquired risk factor for a treatable cause of recurrent pregnancy loss and for pregnancy complications (early and severe pre-eclampsia) [5]. aPL are present in 30–40% of SLE patients and up to a third of these patients (10–15% of all SLE patients) have a clinically overt APS. On the contrary, only few patients with primary APS tend to evolve into full-blown SLE and, usually, this takes place only after a long period of time.

The prevalence of CAPS is low (less than 1% of APS cases), but its potentially lethal outcome emphasizes its clinical relevance. In order to put together all the published case reports as well as the new diagnosed cases from all over the world, an international registry of patients with catastrophic APS ("CAPS Registry") was created in 2000 by the European Forum on Antiphospholipid Antibodies. Currently, it documents the entire clinical, laboratory, and therapeutic data of more than 500 patients.

History

Several reports already in the early 1960s described the association between thrombosis and the LA phenomenon in patients with or without SLE, but the idea of a syndrome was not developed until 1983, when Graham R.V. Hughes linked major cerebrovascular events, abortions, thrombocytopenia, and presence of LA in a famous editorial published in the British Medical Journal [6]. Studies conducted by Drs. Azzudin Gharawi and Nigel Harris in Hughes' laboratory in the early 1980s prompted the development of solid-phase immunoassays to detect aCL [7]. These findings led to the definition of the "anticardiolipin syndrome", which was quickly replaced by APS. The original concept of APS, however, has been expanded over the years and now includes various complications, such as heart valve lesions, adrenal insufficiency, and even avascular bone necrosis, among many others.

Etiology

The exact etiology of APS is not known, but genetic and environmental factors have been implicated. In the first group, the association with HLA-DR4 and DRw53 has been described. Infections are perhaps the most prominent environmental trigger and there is evidence that molecular mimicry can induce the production of pathogenic aPL, presumably because of a breakdown of the mechanisms involved in peripheral tolerance.

Pathophysiology

aPL are heterogeneous antibodies and several mechanisms have been implicated in APS-associated clinical manifestations. aPL can bind to negatively charged phospholipids either directly or via proteins that act as cofactors. β2GPI represents the main antigenic target and along with prothrombin accounts for more than 90% of aPL binding activity in APS patients. Interestingly, β2GPI does not bind to unstimulated endothelium in vivo, and the initiating stimulus that primes endothelium, when not identifiable as in the case of surgery or infections, might be represented by disturbance of the redox balance in the vascular milieu [8].

The binding of aPL to the phospholipids-bound β2GPI leads to its conformational change and dimerization (the immunogenic form of β2GPI); dimerization of β2GPI on the surfaces of endothelial cells, platelets, and monocytes upregulates the expression of prothrombotic cellular adhesion molecules, reduces the response to natural anticoagulants, and activates complement. Furthermore, it antagonizes the activity of endothelial nitric oxide synthase, leading to impaired endothelial nitric oxide-dependent vascular relaxation [1]. Table 2.1 reports possible mechanisms by which aPL may induce thrombosis and pregnancy morbidity in patients with APS.

Table 2.1 Pathogenic mechanisms of aPL

Thrombosis
Inhibition of anticoagulant reactions:
Inhibition of β2GPI anticoagulant activity
Inhibition of the protein C pathway
Inhibition of protein C activation
Inhibition of antithrombin activity
Displacement of annexin A5 shield
Cell-mediated events:
On endothelial cells:
Enhanced endothelial cells' proinflammatory/procoagulant activity
Increased expression of tissue factor/reduced expression of tissue factor pathway inhibitor
Increased expression of adhesion molecules (E-selectin, ICAM-1, VCAM-1)
Increased expression of VEGF
Up-regulation of the mTOR complex
Impaired fibrinolysis
Dysregulation of eicosanoids
Decreased endothelial cell prostacyclin production
Increased platelet thromboxan A2 production
On monocytes
Increased expression of tissue factor
On platelets
Enhanced platelet activation/aggregation
Pregnancy morbidity
Decidua and trophoblast
Abnormal itertrophoblast fusion
Reduced trophoblast invasiveness
Reduced hCG secretion
Abnormal implantation
Reduced angiogenesis
Abnormal spiral artery transformation and maturation
Abnormal endometrial differentiation
Complement activation
Neutrophil recruitment

hCF human chorionic gonadotropin, *ICAM-1* intercellular adhesion molecule-1, *mTOR* mechanistic target of rapamycin, *VCAM-1* vascular cell adhesion molecule-1

Clinical Manifestations

The clinical picture of the APS is characterized thrombosis, pregnancy morbidity, and thrombocytopenia. Single vessel involvement or multiple vascular occlusions may give rise to a wide variety of presentations. Any combination of vascular occlusive events may occur in the same individual and the time interval between them also varies considerably from weeks to months or even years. The "Euro-Phospholipid" project, a prospective study of 1000 European APS patients that started in 1999 as an attempt to describe the epidemiology and the course of APS in real life, has provided accurate information on the prevalence of the majority of clinical manifestations of APS, which are reported in Table 2.2 [9].

Table 2.2 Most common manifestations in APS, according to the "Euro-Phospholipid Project" that includes 1000 European patients with this syndrome (including the cumulative manifestations over 10-year follow-up)

Clinical manifestation	%
Deep vein thrombosis	43.2
Thrombocytopenia (100,000 platelets/μL)	38.3
Livedo reticularis	32.2
Stroke	25.1
Pulmonary embolism	17.6
Cardiac valve thickening/disfunction	16.2
Transient ischemic attack	15.8
Hemolytic anemia	13.7
Superficial thrombophlebitis	13.4
Epilepsy	10.2
Skin ulcers	8.6
Myocardial infarction	7.4
Vegetations	4.8
Obstetric manifestations (per tot n of pregnancies)	
Preeclampsia/eclampsia	11.6
Fetal manifestations (per tot n of pregnancies)	
Early fetal loss (before tenth week)	51.9
Late fetal loss (after tenth week)	21.7
Premature birth	58.2
Intrauterine growth restriction	27.8

Laboratory Abnormalities

A wide variety of laboratory abnormalities can be found in patients with APS, depending on different organ involvement. The most common immunological features are depicted in Table 2.3. LA testing must be performed according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on Lupus Anti-coagulants/Phospholipid-Dependent Antibodies) [10].

Table 2.3 Most common immunological findings in the APS, according to the "Euro-Phospholipid Project"

Immunological feature	%
aCL	87.9
IgG and IgM	32.1
IgG alone	43.6
IgM alone	12.2
LA	53.6
LA alone	12.1
LA and aCL	41.5
Antinuclear antibodies	59.7
Anti-dsDNA	29.2
Anti-Ro/SS-A	14
Anti-La/SS-B	5.7
Anti-RNP	5.9
Anti-Sm	5.5
Rheumatoid factor	7.8
Cryoglobulins	3.6

Diagnosis of APS

As a general rule, APS must be suspected in a young patient presenting with unprovoked thrombosis, especially if at unusual sites and recurrent, or in case of thrombotic or pregnancy complications associated with other autoimmune diseases. Unexplained prolongation of the activated partial thromboplastin time (aPTT), *livedo reticularis or racemosa*, and mild thrombocytopenia are clues for suspecting APS. The clinical picture is not constant and ranges from asymptomatic aPL carriers to recurrent arterial and/or venous thrombosis, recurrent pregnancy loss, or isolated "non-criteria" manifestations (which stands for manifestations not included in the Sydney classification criteria).

Since diagnostic criteria for APS are lacking, diagnosis is made through the combination of clinical and laboratory findings. With the aim of setting up homogenous cohorts for research purposes, several classification criteria have been developed over the years. The first consensus criteria were formulated during a workshop held at the 8th International Symposium on aPL held in Sapporo, Japan, in 1998. The Sapporo criteria, as they are often called, were revised during another workshop in Sydney, Australia, in 2004, at the 11th International Congress on aPL, and published as a consensus statement in 2006. These new criteria included the aβ2GPI, which were absent in the first consensus. At least one clinical (vascular thrombosis or pregnancy morbidity) and one laboratory (positivity for aCL, aβ2GPI or LA in at least two occasions at least 12 weeks apart) criterion had to be met for the classification of APS. No less than 12 weeks and no more than 5 years could separate the clinical manifestation and the positive aPL test. Patients were stratified according to the presence of risk factors for thrombosis (e.g., arterial hypertension, dyslipidemia, malignancies, oral contraceptives, congenital thrombophilia…) to provide a more uniform basis in selecting patients for research purpose. Some clinical features, such as cardiac valve involvement, *livedo reticularis*, thrombocytopenia, APS nephropathy, and non-thrombotic central nervous system manifestations (i.e., migraine, myelopathy, cognitive dysfunction) were remarked on, but not included among clinical criteria, that remained unchanged. Finally, patients were classified into four subcategories according to the possible combinations of aPL positivity [11]. While the Sapporo criteria were prospectively validated in a cohort of patients with APS, SLE and SLE-like conditions, finding a sensitivity, specificity, positive predictive value, and negative predictive value of 0.71, 0.98, 0.95, and 0.88, respectively, the discriminatory capacity of the Sydney criteria has never been tested.

Over the past decade, substantial evidence has accumulated on different clinical and laboratory issues related to APS. Moreover, new methodologically rigorous and data-driven approaches to address biases and develop a robust set of classification criteria have been published [12]. Starting from these premises, an international effort to develop new classification criteria, which was jointly supported by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR), recently led to the publication of new APS criteria [13]. Similar to SLE classification criteria, these criteria include an entry criterion of at least one positive aPL within 3 years of identification of a clinical criterion, followed by additive weighted criteria clustered into 6 clinical and 2 laboratory domains. Moreover, these new criteria take into account risk factors for venous and arterial thrombosis, determining differential punctuation for clinical criteria accordingly. Regarding laboratory criteria, a lower value is given to IgM compared to IgG, and IgG moderate and high positivity score differently. Finally, at least three points from each domain are requested for patient classification (see Table 2.4). Those new criteria have been tested in a validation cohort showing a sensitivity of 0.84 and a specificity of 0.99.

The preliminary classification criteria for catastrophic APS were formulated at a workshop in Taormina, Italy, in 2002, during the 10th International Congress on aPL, and published as a consensus statement in 2003 [14]. These criteria have been validated in a cohort of patients with CAPS, APS, and SLE, showing a sensitivity of 90.3%, a specificity of 99.4%, a positive predictive value of 99.4%, and a negative predictive value of 91.1% [15].

Sometimes a high clinical suspicion of APS is not supported by concomitant positivity of aPL assays included in the serological criteria for APS, which are persistently negative. This is the framework of the so-called seronegative APS, described for the first time in 2003. Thenceforth, numerous investigators looked for the presence of aPL in

Table 2.4 EULAR/ACR APS classification criteria

Entry Criteria
At least one documented clinical criterion listed below
plus
a positive aPL test (LA, moderate/high titer aCL or aβ2GPI IgG or IgM)
within 3 years of the clinical criterion

If absent, do not attempt to classify as APS—If present, apply additive criteria

Additive clinical and laboratory criteria
Do not count a clinical criterion if there is an equally or more likely explanation than APS
Within each domain, only count the highest weighted criterion towards the total score

Clinical domains and criteria	**Weight**		**Weight**
D1. Macrovascular (Venous Thromboembolism [VTE])		**D2. Macrovascular (Arterial Thrombosis [AT])**	
VTE with a high-risk VTE profile	1	AT with a high-risk CVD profile	2
VTE without a high-risk VTE profile	3	AT without a high-risk CVD profile	4
D3. Microvascular		**D4. Obstetric**	
Suspected (one or more of the following)	2	≥3 Consecutive pre-fetal (<10 weeks) and/or early fetal (10 weeks 0 day to 15 weeks 6 days) deaths	1
Livedo racemosa (exam)			
Livedoid vasculopathy lesions (exam)			
Acute/chronic aPL-nephropathy (exam or lab)		Fetal death (16 weeks 0 day to 33 weeks 6 days) in the absence of pre-eclampsia (PEC) with severe features or placental insufficiency (PI) with severe features	1
Pulmonary hemorrhage (symptoms and imaging)			
Established (one of more of the following)	5		
Livedoid vasculopathy (pathology)		PEC with severe features (<34 weeks 0 day) or PI with severe features (<34 weeks 0 day) with/without fetal death	3
Acute/chronic aPL-nephropathy (pathology)			
Pulmonary hemorrhage (BAL or pathology)			
Myocardial disease (imaging or pathology)			
Adrenal hemorrhage (imaging or pathology)		PEC with severe features (<34 weeks 0 day) and PI with severe features (<34 weeks 0 day) with/without fetal death	4
D5. Cardiac Valve		**D6. Hematology**	
Thickening	2	Thrombocytopenia (lowest 20–130 × 10^9/L)	2
Vegetation	4		
Laboratory (aPL) domains and criteria	**Weight**		
D7. aPL test by coagulation functional assay (lupus anticoagulant test [LAC])		**D8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β2-glycoprotein-I antibody [aβ2GPI] ELISA [persistent])**	
Positive LAC (single—one time)	1	Moderate or high positive(IgM) (aCL and/ or aβ2GPI)	1
Positive LAC (persistent)	5	Moderate positive(IgG) (aCL and/or aβ2GPI)	4
		High positive (IgG) (aCL or aβ2GPI)	5
		High positive (IgG) (aCL and aβ2GPI)	7

TOTAL SCORE
Classify as Antiphospholipid Syndrome for research purposes if there are at least 3 points from clinical domains AND at least 3 points from laboratory domains

these patients not included in the serological criteria for APS. For instance, these non-criteria antibodies include aCL and aβ2GPI IgA, antibodies specific to phospholipid-binding plasma (cofactor) proteins (such as phosphatidylethanolamine, prothrombin, protein C, protein S, annexin II and V, and domain I of β2GPI), phospholipid–protein complexes (particularly vimentin–cardiolipin complexes), and anionic phospholipids other than cardiolipin (including phosphatidylserine, phosphatidylinositol, and phosphatidic acid). In case of highly suspected APS with persistently negative LA, aCL, and anti-β2GPI IgG and IgM, after ruling out other causes of thrombophilia, looking for these non-criteria antibodies can hint the diagnosis.

Therapy and Prevention

The elimination of aPL through immunosuppression is usually temporary, and aPL usually return within 3 weeks from stopping treatment. Therefore, therapy should not primarily be directed at reducing or suppressing aPL levels and the use of immunotherapy is generally not indicated, unless required for the treatment of the underlying condition, e.g., SLE, or in acute life-threatening situations, such as the catastrophic APS.

The mainstay of treatment of thrombotic APS is oral anticoagulation with vitamin K antagonists (VKA) with a target INR between 2 and 3. Indefinite anticoagulation in patients with unprovoked arterial or venous thrombosis is highly warranted, due to the high risk of thrombosis recurrence in case of VKA discontinuation [16]. However, when the initial thrombotic event is "triggered" by a drug (e.g., oral contraceptives) or trauma, long-term anticoagulation may not really be necessary and antiaggregants, as well as avoidance of the triggering factors, may indeed be sufficiently effective for future thromboprophylaxis. High-quality evidence to support any management strategy when warfarin therapy fails despite a target INR is lacking. Viable options include higher intensity warfarin therapy (target INR, 3–4), switch to LMWH, the addition of LDA, antimalarials, statins, or a combination of these approaches.

Direct oral anticoagulants (DOAC) are not recommended in APS, especially for high-risk patients with triple positivity and previous arterial thrombosis, due to results of three randomized trials, two with rivaroxaban and one with apixaban, that showed higher rate of thrombosis recurrence in such patients in comparison to VKA [17].

A prompt and aggressive treatment is critical in case of catastrophic APS, and the current standard of care is the so-called triple therapy, a combination of anticoagulants, glucocorticoids, and plasma exchange. Intravenous immunoglobulins (1–2 g/kg, given over a period of 2–5 days) are often associated with the triple therapy and, as well as rituximab. Eculizumab, a humanized monoclonal antibody directed against the C5 protein of complement cascade, preventing the generation of the terminal complement complex C5b-9, has also been used with success in refractory cases [1].

In patients with aPL who have never suffered from a thrombotic event (primary thromboprophylaxis), energetic attempts must be made to avoid or to treat any associated risk factors—e.g., antihypertensives, cholesterol-lowering agents, treatment of active nephritis, avoidance of smoking or sedentarism, etc. Care should be also taken with the administration of oral contraceptives. The use of low-dose aspirin in patients with high-risk aPL profile, concomitant SLE, or obstetric APS outside of pregnancy, is indicated as per current EULAR treatment guidelines, due to the results of numerous observational studies, although an underpowered clinical trial did not show efficacy [16]. Prophylaxis of venous thrombosis, with nontherapeutic dose of low-molecular-weight heparin, is required for patients undergoing surgical procedures (particularly hip surgery), those with prolonged bedbound, or before long flights.

The cornerstone of treatment to prevent pregnancy complications in women with previous obstetric APS is the combination of LDA and a prophylactic dose of unfractionated heparin (UFH) or LMWH. LDA should be preferably started prior to conception, and heparin should be added as soon as pregnancy is confirmed and continued up to 6 weeks after delivery to prevent maternal thrombosis, given the increased thromboembolic risk in puerperium. Oral anticoagulants should be discontinued at conception because of teratogenicity between 6 and 14 weeks of gestation [16]. Table 2.5 reports EULAR treatment recommendations for thrombotic (a) and obstetric (b) APS, respectively, according to different clinical scenarios [16].

Table 2.5 Treatment recommendations for thrombotic and obstetric APS, respectively, according to different clinical scenarios following EULAR guidelines [16]

(a) **Treatment of thrombotic APS according to different clinical scenarios**	
Primary Thromboprophylaxis	
1. Asymptomatic aPL carriers (not fulfilling any vascular or obstetric APS classification criteria) with a high-risk aPL profile with or without traditional risk factors *2. SLE with aPL (especially those with a high-risk aPL profile) and no history of thrombosis* *3. History of obstetric APS outside pregnancy*	*LDA (75–100 mg per day)*
Secondary thromboprophylaxis	
1. Definite APS and first venous thrombosis	
(a) Unprovoked: indefinite anticoagulation	*VKA with a target INR 2–3*
(b) Provoked: short-term anticoagulation (3–6 months)	
2. Definite APS and first arterial thrombosis	*VKA with a target INR 2–3 (INR 3–4 in selected cases)*
3. Definite APS and recurrent venous thrombosis despite treatment with VKA with target INR 2–3	*VKA with a target INR 3–4* *Or* *LMWH (therapeutic dose)* *Or* *VKA + LDA ± HCQ*
Catastrophic APS	*Glucocorticoids, UFH, Pex, IVIG, Rituximab, Eculizumab (refractory)*
(b) Treatment of obstetric APS according to different clinical scenarios	
Asymptomatic carriers of aPL	*LDA (75–100 mg per day)*
Obstetric APS	
1. More than three miscarriages (before 10th week of gestation) or at least one fetal loss (after 10th week)	*LDA + prophylactic LMWH*
2. Delivery before 34th week because of preeclampsia, eclampsia, placental insufficiency	*LDA ± prophylactic LMWH*
3. History of thrombotic APS	*LDA + therapeutic LMWH*
Recurrent obstetric APS despite treatment	*LDA + therapeutic LMWH ± HCQ ± low dose prednisolone (first trimester)*

High-risk profile: the presence of LA, or of double (any combination of LA, aCL, or anti-β2-GPI antibodies) or triple (all three subtypes) aPL positivity in 2 or more occasions at least 12 weeks apart, or the presence of persistently high aPL titers

Low-risk profile: isolated aCL or aβ2GPI antibodies at low-medium titers, particularly if transiently positive

LDA must be started before conception and LMWH must be continued up to 6 weeks after delivery in case of pure obstetric APS. If history of thrombosis, switch VKA to LMWH as soon as pregnancy is confirmed and switch back to VKA after delivery

Risk Stratification

Recurrence of clinical manifestations is a main concern in APS, a condition that is usually diagnosed in young people with a long life expectancy. Known risk factors for thrombotic recurrence are a previous arterial thrombosis, high-risk aPL profiles such as triple aPL positivity and LA positivity, association with SLE and presence of concomitant genetic and acquired risk factors for thrombosis (such as arterial hypertension, dyslipidemia, smoking, diabetes mellitus, oral contraceptives, menopause, etc.).

Besides the aforementioned drivers, clinical events are triggered by aPL's persistent presence over time [18]. In recent years, two score systems have been proposed as risk stratification tool for clinical manifestations in aPL-positive patients. The aPL-score (aPL-S) is a complex score based solely on the aPL profile (including the three criteria aPL plus anti-phosphatidylserine/prothrombin), and the Global APS Score takes into account the aPL profile plus cardiovascular risk factors, namely arterial hypertension and dyslipidemia. Both have shown to be useful tools to diagnose the disease and to predict thrombotic recurrence [19, 20].

Conclusions

APS is the most common acquired thrombophilia. Historically, diagnosis was based on the presence of thrombosis and pregnancy morbidity as the main clinical manifestations in association with aPL. The new EULAR/ACR classification criteria highlighted the importance of some formerly defined "non-criteria" manifestations, such as thrombocytopenia and cardiac valve involvement (which is a sufficient clinical criterion in the presence of vegetation). Moreover, they increased the specificity of the former ones by differentiating the weight of different aPL. Nevertheless, EULAR/ACR criteria are high-specificity criteria specifically designed for research purposes and should not be used for diagnosing the disease.

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3

Rheumatoid Arthritis

Virginia Ruiz-Esquide and José A. Gómez-Puerta

Abstract

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease. It is characterized typically by a symmetric polyarthritis that can be destructive and disabling, and in some occasions, extra-articular manifestations, making RA a heterogeneous disease. The diagnosis is based on clinical assessment and can be supported by serological markers and imaging. Early diagnosis and treatment of RA can slow the disease progression and prevent disability. New drugs and treatment strategies have improved disease outcomes.

Keywords

Rheumatoid arthritis · Early arthritis · Classification criteria · Anti-cyclic citrullinated peptide antibodies (ACPA)

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease of a not well-known etiology, characterized by chronic polyarthritis. This polyarthritis typically affects small and medium-sized joints, is progressive, and, without treatment, can lead to joint destruction and disability. In addition, extra-articular manifestations are frequently present, which makes RA a systemic and heterogenous disease that can sometimes be difficult to treat and usually needs chronic treatment with disease-modifying antirheumatic drugs (DMARD).

Epidemiology

RA is a world-wide distributed disease, more frequent in women than in men, with a female-to-male sex ratio of 3:1 to 2:1. It can affect people of any age, but peak onset is between 50 and 60 years of age (sudden decline of estrogens might be a risk factor). In the reporting of the Global Burden of Disease (GBD) 2017 the global prevalence of RA was found to be 0.27% (95% CI 0.24–0.3%) [1]. But some publications reported a higher prevalence. A meta-analysis published in 2021 analyzed a total of 60 population-based studies from 41 countries and observed a pooled prevalence of RA of 0.46 (95% CI 0.35–0.57%). This may be due to different inclusion criteria in the analysis [2]. This prevalence varies globally. Generally, a higher prevalence is observed in industrialized countries and urban settings. This may be explained by different environmental exposures to pollution, genetic, and other factors. In northern and western Europe countries the prevalence of RA is about 0.40%, with 20–30 new cases per 1,000,000 patient-years and in southern European countries it is approximately 0.20%, with an incidence of 7–15 new cases per 100,000 patient-years. In North America, the prevalence reported is 0.38% [3]. According to the GBD 2017 report, the incidence and prevalence, as well as the age at disease onset, is increasing over time, but mortality and time between diagnosis and initiation of DMARD are observed to be decreasing over time [3].

Mortality rates are increased in RA patients. It is estimated to be approximately 1.5 times higher than in the general population but has decreased over the last decades. The most frequent causes of death are cardiovascular disease, lung disease, and infections [4].

Risk Factors

As with other autoimmune diseases, RA is favored by a combination of genetic and environmental factors that, when present, increase the risk to develop the disease.

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Genetic Risk Factors

Family and twin studies have shown that there is a higher risk of developing RA if you have a close relative with the condition, it is estimated that the genetic variation accounts for 50–60% of the risk of RA [5]. The most well-studied genetic factor is the HLA (human leukocyte antigen) region, specifically the HLA-DRB1 gene. Specific variations of this gene, known as HLA-DRB1 shared epitope alleles (the HLA-DRB1*01, *04, and *10 alleles), are the strongest genetic risk factor for RA development, especially for ACPA-positive RA. These alleles contribute to the immune system's improper recognition of self-tissues, triggering an autoimmune response.

Besides HLA-DRB1, other genes have been implicated in RA susceptibility, including PTPN22, TNFα, PADI4, STAT4, CTLA4, TRAF1-C5, and others. These genes are involved in various aspects of the immune response and regulation [6].

Epigenetic changes, such as DNA methylation and histone modifications, can also influence the development of RA. Epigenetic modifications can affect gene expression and play a role in immune system function and response to inflammation.

Environmental Risk Factors

While genetics play a significant role, environmental factors such as infections, smoking, and hormonal changes can also contribute to the development of RA. These environmental factors interact with a genetic predisposition to trigger the autoimmune response seen in RA.

Smoking is the most recognized and important environmental risk factor for RA, in particular for ACPA-positive RA. Up to 25% of the risk of seropositive RA may be attributed to smoking [7]. Tobacco smoking leads to a higher expression of PAD2 enzyme and an increase in protein citrullination. This higher citrullination, in the context of genetic susceptibility, by mechanisms not yet well known may increase the risk of ACPA production. Air pollution and some inhaled particulates such as silica, asbestos, and textile-dust are well associated with the development of RA.

The microbiome of the oral cavity and gut has long been studied about RA risk. RA patients have been observed to have differences in their microbiome in comparison to healthy controls. Differences in bifidobacterial species, clostridium, and lactobacillus have been reported in gut microbiota [8]. This gut dysbiosis has been hypothesized to contribute to local inflammation, loss of barrier function, bacterial translocation, and trigger of immune response and immune system dysfunction [9]. RA has also been epidemiologically associated with periodontitis in multiple studies. Periodontitis is a chronic inflammation of gums caused by *Porphyromona gingivalis*. This microorganism expresses a PAD enzyme and induces protein citrullination and a pro-inflammatory environment.

Other environmental factors such as nutrition and diet, and vitamin D have extensively been studied. An increased dietary intake of omega-3 polyunsaturated fatty acids has been reported to reduce the risk of RA and improve disease activity in RA patients. Low levels of vitamin D and some polymorphisms in the vitamin D receptor (VDR) with an increased risk of RA development in some studies, but this is still controversial. Vitamin D has an immunomodulating role, it contributes to the regulation of T cells, macrophage response, and its antigen-presenting activity.

Clinical Presentation

RA is a complex and heterogeneous disease, with variable clinical presentation. The most relevant clinical manifestation is joint involvement. RA is typically a symmetric polyarticular disease, that usually involves small joints of hands and feet, with swelling and pain of wrists, metacarpophalangeal and proximal interphalangeal joints of hands, and metatarsophalangeal joints in the feet. Even though this is the most frequent pattern of joint involvement, large joints can be involved as well, such as ankles, knees, elbows, shoulders, or hips. Large joint involvement may more frequently have a non-symmetric pattern. Small distal interphalangeal joints are rarely affected. Joint involvement is characteristically accompanied by morning stiffness lasting more than 30 min, lasting frequently several hours, and fatigue.

Along with joint manifestations, extra-articular manifestations may be also present. The reported frequency of the extra-articular manifestations varies in different cohorts, between 20% and 40%. These manifestations increase significatively the morbidity and mortality of RA. Their development is reported to be associated with long-term seropositive disease, disability, and persistent inflammatory activity, but they can present at early stages of disease or even at disease onset. Rheumatoid nodules are the most commonly reported extra-articular feature and are present in up to 30% of patients. Other frequent extra-articular manifestations are sicca syndrome and pulmonary involvement (6–10%). Less frequent are other extra-articular manifestations such as vasculitis, neuropathy, serositis, episcleritis, scleritis, glomerulonephritis, secondary amyloidosis, and Felty syndrome [10].

Road from pathogenesis to clinical manifestations is summarized in Fig. 3.1.

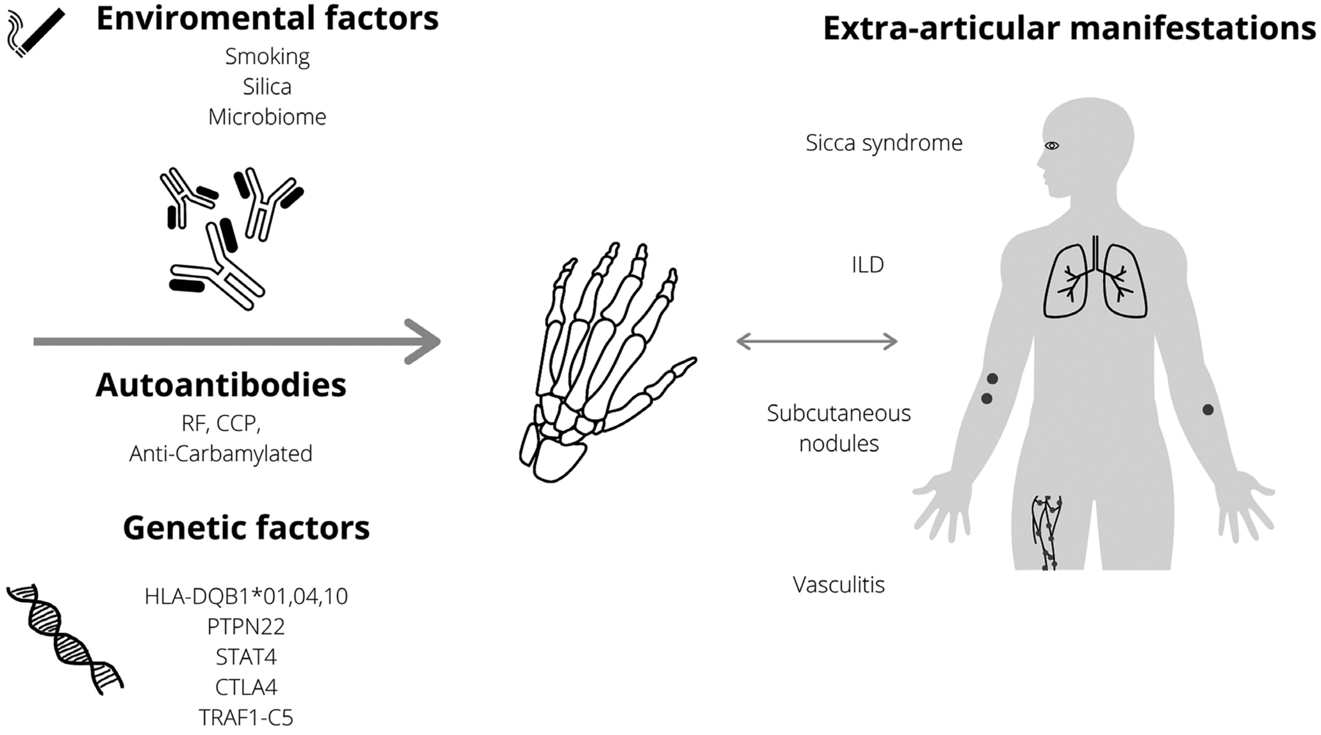

Fig. 3.1 Road from pathogenesis to clinical manifestations in RA. *ILD* interstitial lung disease, *RF* rheumatoid factor, *CCP* cyclic citrullinated peptide

Serological Features and Autoantibodies

Serological testing, along with clinical examination, plays an important role in diagnosing and managing RA.

Acute Phase Reactants

Classical acute phase reactants, such as erythrocyte sedimentation rate (ESR) and reactive C protein (CRP), are serum biomarkers that are frequently used as diagnostic tools as well as indicators of disease activity and treatment response in autoimmune diseases. These are nonspecific markers of inflammatory response. IL6 and TNF-α are more specific biomarkers of RA activity, but are not commonly used in clinical practice. More recently calprotectin is being investigated as a promising biomarker in RA. Calprotectin has been demonstrated to play a critical role in the pathogenesis of RA, as a trigger of chemotaxis, phagocyte migration, and modulation of neutrophils and macrophages. Higher calprotectin levels have been found in synovial fluid, plasma, and serum from RA patients; it has also been demonstrated to be a good correlation of calprotectin plasma levels with disease activity and good sensitivity to change in response to treatment [11].

Autoantibodies

Rheumatoid factor (RF) and anti-citrullinated antibodies (ACPA) are the classic and most important autoantibodies detected in RA. It is estimated that between 50% and 80% of RA patients have one or both autoantibodies present. This has permitted the identification of two different subgroups of patients: seropositive and seronegative RA, who have different characteristics.

RF has a sensitivity of 78% and a specificity of 80% and may be present in low prevalence in healthy subjects, increasing with age up to 25% in elderly adults over 85 years of age; and in other autoimmune of inflammatory diseases. ACPA antibodies have demonstrated similar sensitivity (75%) with a much higher specificity, (97%) [12].

More recently other autoantibodies against other post-transcriptional modified proteins have been identified. The most studied are anti-carbamylated protein (anti-CarP) antibodies, present in about 45% of RA patients, and anti-acetylated protein antibodies, which have been described in approximately 40% of RA patients, mainly in ACPA-positive subjects. Currently, these new autoantibodies are not used in clinical practice, but their study is providing new insights into the pathophysiology of RA [13].

Autoantibodies are present years before signs and symptoms of RA became evident. This state is known as “Pre-RA” and can start more than 10 years before the presentation of RA symptoms. This time of pre-RA reveals the role of the adaptative immune system in the pathogenesis of RA (ACPA-positive RA). During this time, autoantibodies go through affinity maturation, epitope spreading, isotype change, and progressive increase in titers process, leading finally to the clinically detectable disease [14]. During recent years, the study of this pre-RA period has given light to a better understanding of the pathology of RA and is currently a subject of active investigation as an opportunity of early treatment in the hope that it may enable a change in the entire course of the disease, even though this is currently under study and will need further investigation [15].

The early presence of ACPA antibodies together with their higher specificity makes them a useful tool for RA diagnosis and were included in the latest RA classification criteria of 2010.

Diagnosis of Rheumatoid Arthritis

RA, as mentioned before, is a heterogeneous disease. There are no diagnostic criteria, and the diagnosis of RA is a process led by the specialist based on clinical manifestations and complementary tests. In early stages, RA may be oligosymptomatic, with just one or a few joints involved, with normal acute phase reactants and negative autoantibodies. To help the diagnosis, subclinical arthritis or synovial inflammation can be detected with the help of imaging techniques such as ultrasonography or MRI. There are classification criteria that, even though they were developed for the identification of homogenous patient populations for clinical trials and studies, may as well help in the establishment of the diagnosis of RA. Until 2010 the criteria available were those published in 1987 by the American College of Rheumatology. These criteria included the presence of three or more involved joints, subcutaneous nodules, and typical erosive disease (among other criteria). These characteristics are descriptive of established disease. In 2010 the American College of Rheumatology/European League Against Rheumatism proposed a new set of criteria. One of the main objectives of this new criteria was to be able to classify patients with RA at earlier stages of the disease. To apply these criteria the first step is to consider the target population. This criteria can only be applied if the subject has at least one joint with definite clinical synovitis (swelling) and this synovitis cannot be better explained by another disease. The author emphasizes that synovitis must be detected on clinical examination but explains that this may change in the future as validated imaging techniques become more widely available. Then four additional criteria can be applied (shown in Table 3.1), and at least six out of ten points have to be scored to identify those subjects with “definite RA”. Patients with a score of less than six out of ten are not classifiable as having RA, but their status can be reassessed, and the criteria might be fulfilled cumulatively over time. The first criteria consider the joint involvement (swollen of tender joint on examination, which may be confirmed by imaging for evidence of synovitis), and scores 0–5 depending on the number of joints involved and if they are small or large joints. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from the assessment. Large joints refer to shoulders, elbows, hips, knees, and ankles. Small joints refer to the metacarpophalangeal joints, proximal interphalangeal joints, second to fifth metatarsophalangeal joint, thumb interphalangeal joint, and wrists. The second criteria consider the autoantibodies, scoring 0–3, taking into account the positivity and if they are low or high levels of autoantibodies. The third criteria take into account the symptom duration (as reported by the patient, symptoms of pain, swelling of tenderness), with 0 point if it is under 6 weeks and 1 point if it is 6 weeks or longer. Finally, the fourth criteria consider the presence of acute phase reactants, scoring 1 point if CRP or ESR are abnormal (over the limit of local laboratory standard) and 0 if they are normal. These criteria aimed to classify newly presenting patients, patients with erosive disease typical of RA and with a history compatible with prior fulfillment of these criteria should also be classified as having RA [16]. These criteria were validated in multiple cohorts, and they have been shown to achieve the goal of earlier clas-

Table 3.1 Rheumatoid arthritis classification criteria

Target population: patients who have at least one joint with definite clinical synovitis (swelling) and with the synovitis not better explained by another disease	
Classification	Points
Joint distribution	
1 large joint	0
2–10 large joints	1
1–3 small joints (large joints are not counted)	2
4–10 small joints (large joints are not counted)	3
>10 joints (≥1 small joint)	5
Serology	
Negative RF and negative ACPA	0
Low positive RF of low positive ACPA	2
High positive RF of high positive ACPA	3
Symptom duration, weeks	
<6	0
≥6	1
Acute phase reactants	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1

ACPA anticitrullinated peptide antibodies, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *RF* rheumatoid factor

≥6 patients classified as definite RA

sification of RA, with increased sensitivity over the previous criteria. But this is at the price of loss of specificity, special attention must be drawn to the exclusion of another diagnosis when applying these 2010 RA classification criteria. Their indiscriminate or inappropriate use may carry the risk of overdiagnosis and overtreatment [17].

Prognosis and Treatment

RA is a chronic disease, progressive and disabling if untreated. Early diagnosis and treatment prevent irreversible disability. In the last 20 years, new drugs and treatment strategies have radically changed the prognosis of the disease, making disease remission a achievable goal.

Disease-Modifying Antirheumatic Drugs (DMARD)

There are three different groups of DMARD. The first one is the classical synthetic DMARD (csDMARD) that includes methotrexate (MTX), leflunomide, sulfasalazine, and chloroquine/hydroxychloroquine. The second group is the biologic DMARD (bDMARD) that includes five TNFα inhibitors (infliximab, etanercept, adalimumab, golimumab, and certolizumab), two IL-6 inhibitors (tocilizumab and sarilumab), abatacept (selective co-stimulator of CD80/86), and rituximab (anti-CD20). In recent years biosimilars of some of these biologic DMARDs have been approved. And the third group is the targeted synthetic DMARD (tsDMARD), there are five of them approved in different countries, tofacitinib, baricitnib, perficitinib, upadacitinib, and filgotinib, but many more are under investigation and may in future years enlarge this group of tsDMARD.

Treatment Strategy

The use and benefit of all this therapeutic armamentarium is best drawn by early treatment. The prognosis of RA is best when treatment is started in the early stages of the disease, during the “window of opportunity”. This treatment thereafter must be adjusted and changed according to disease activity in a “treat to target” strategy. Guidelines recommend starting treatment as early as possible with conventional synthetic DMARD (which are considered first-line therapies), usually MTX. Other csDMARD can be used if MTX is not tolerated or cannot be used. It may be combined with glucocorticoids in a low dose and for as short period of time as possible. If target of remission or low disease activity is not achieved treatment is progressed to a second stage, meaning changing or adding a bDMARD or tsDMARD. Disease activity should be reassessed periodically, and treatment adjusted, always with the objective of achieving disease remission or, if this is not possible, low disease activity (the treat-to-target strategy) [18, 19].

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4

Juvenile Idiopathic Arthritis

Eli M. Eisenstein and Yackov Berkun

Abstract

Juvenile idiopathic arthritis (JIA) refers to a group of immune-mediated disorders first appearing before 16 years of age, that share in common joint inflammation as their main clinical manifestation. The 2001 International League of Associations for Rheumatology (ILAR) classification defines seven sub-types of JIA. However, a number of shortcomings have been identified in the ILAR classification, including the tenuous nature of the biologic distinctions between certain subtypes, and lack of integration with classifications widely used for adults with rheumatic disease. Accordingly, the Pediatric Rheumatology International Trials Organization (PRINTO) has published a revised, draft classification, which partially addresses some of these issues. It is expected that classification of pediatric arthritis will evolve further as understanding of the genetic and immune mechanisms underlying the different forms of chronic arthritis in childhood advances.

Keywords

Juvenile idiopathic arthritis · Diagnostic criteria · Classification criteria · Biologic classification · PRINTO JIA classification

Introduction

JIA is a diagnosis based on signs of inflammation involving one or more joints lasting 6 or more weeks, in a child less than 16 years of age. While symptoms may begin acutely, in some cases disease presentation is insidious, with relatively mild arthralgia. As a result, diagnosis may be delayed, particularly in young children who may be developmentally limited in their capacity to communicate their symptoms. Arthritis is ascertained based mainly on clinical examination, sometimes supplemented by ultrasound or MRI imaging. With the exception of the systemic form of disease, fever is typically absent in JIA. The diagnosis is one of exclusion, which is assigned after other possible diagnoses are ruled out by history, physical examination, and appropriate imaging and laboratory tests [1, 2].

Pediatric rheumatologists have long recognized that JIA is not a single disease, but rather comprises a group of conditions, with varied pathophysiologic mechanisms, natural history, and associated extra-articular manifestations. These observations are consistent with both murine models of arthritis [3, 4], and rare monogenic forms of arthritis in humans [5, 6], which have shown that disparate immunologic mechanisms can lead to joint inflammation early in life. However, the current understanding of the genetic, immunologic, epigenetic, and environmental basis of the different forms of JIA is far from complete. The classification of JIA into sub-types can best be described as an ongoing project. It now appears that one sub-type of JIA probably represents a distinct, typically pediatric-onset disorder, while other sub-types of JIA are likely to be fundamentally indistinct from idiopathic forms of arthritis that can begin throughout life.

Chronic arthritis occurs less commonly in children than in adults. Overall prevalence in different studies ranges from 15 to 400/100,000, and the disease appears to be more common in northern Europe as compared to other regions [7]. Incidence and prevalence both vary according to disease subtypes. Risk for various forms of disease also varies according to ethnicity: oligoarticular JIA is the most common form of the disease in most areas of the world, except in southeast Asia, where enthesitis-related arthritis and systemic JIA appear to be more common [8].

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The International League of Associations for Rheumatology (ILAR)-2001 JIA Classification

The current standard JIA classification was developed by expert consensus by the ILAR and most recently revised in 2001 [9]. It effectively supplanted previous diagnostic criteria for chronic arthritis in childhood, including the Juvenile Rheumatoid Arthritis and Juvenile Chronic Arthritis systems. It divides JIA into six separate categories based on the number of joints affected, extra-articular manifestations, family history, and limited laboratory testing. The main clinical and laboratory features of each ILAR category are shown in Table 4.1. In addition to positive criteria, and in order to ensure that the categories are mutually exclusive, the ILAR classification also contains exclusion criteria for each category. Patients who do not meet criteria for any of these subtypes, or meet criteria for more than one subtype are defined as a seventh sub-type, "undifferentiated arthritis."

Oligoarticular JIA occurs mainly in young girls, with a peak incidence between 2 and 3 years of age. Asymmetric involvement of large joints is typical, by definition involving up to four joints during the first 6 months of disease. Antinuclear antibodies (ANA) can be found in most patients [10]. Because the specificity of these ANA is unknown, they can be detected by immunofluorescence, but not by antigen-specific multiplex assay. Children with oligoarticular JIA are at high risk for uveitis, which is usually anterior and asymptomatic. Therefore, frequent ophthalmologic screening is an essential component of the management of children with this form of disease.

Table 4.1 International League of Associations for Rheumatology (2001) subtypes of JIA

Subtype	Diagnostic criteria	Laboratory criteria	Exclusions
Systemic arthritis	Arthritis on one or more joints with or preceded by fever for ≥2 weeks, quotidian of at least 3 days, with ≥of: 1. Evanescent rash 2. Generalized lymphadenopathy 3. Hepato/splenomegaly 4. Serositis		a, b, c, d
Oligoarthritis	Arthritis affecting 1–4 joints during the first 6 months of the disease		a, b, c, d, e
Polyarthritis RF negative	Arthritis affecting 5 or more joints during the first 6 months of disease, plus laboratory criterion	Negative test for RF	a, b, c, d, e
Polyarthritis RF positive	Arthritis affecting 5 or more joints during the first 6 months of disease, plus laboratory criterion	2 or more (+) tests for RF at least 3 months apart during the first 6 months of the disease	a, b, c, e
Psoriatic arthritis	Arthritis and psoriasis, and at least two of the following: 1. Dactylitis 2. Nail pitting or onycholysis 3. Psoriasis in a first-degree relative		b, c, d, e
Enthesitis-related arthritis	Arthritis and enthesitis, OR Arthritis or enthesitis plus ≥two of the following: 1. SI tenderness or inflammatory back pain 2. Laboratory criterion 3. Male >6 years of age 4. Acute anterior uveitis 5. AS, enthesitis-related arthritis, sacroiliitis with IBD, RS, or acute anterior uveitis in a first-degree relative	Presence of HLA-B27 antigen	a, d, e
Undifferentiated arthritis	Arthritis that fulfills criteria in no category, or in two or more of the above categories		

Exclusions: (a) Psoriasis or a history of psoriasis in the patient of first-degree relative. (b) Arthritis in an HLA-B27 positive male beginning after the sixth birthday. (c) AS, enthesitis-related arthritis, SI with IBD, RS, or acute anterior uveitis, or a history of one of these disorders in a first-degree relative. (d) The presence of IgM-RF on at least two occasions at least 3 months apart. (e) The presence of systemic JIA in the patient

RF rheumatoid factor, *AS* ankylosing spondylitis, *IBD* inflammatory bowel disease, *SI* sacroiliac, *RS* Reiter's syndrome

Polyarticular RF-negative JIA is defined as arthritis affecting five or more joints during the first 6 months of disease, with negative blood testing for rheumatoid factor (RF). It is similar to oligoarticular JIA in that it also affects mainly young girls, and may be associated with ANA and increased risk for uveitis. On the basis of these similarities, it was suggested that oligoarticular JIA and polyarticular RF-negative JIA subtypes may represent a spectrum of a single disease. However, there appear to be differences between the two regarding prevalence of ANA and uveitis, as well as certain HLA associations.

Rheumatoid factor (RF)-positive JIA occurs infrequently in childhood. It typically affects girls, with symmetrical involvement of large and small joints. This disease is considered the childhood-onset equivalent of adult-onset RF-positive rheumatoid arthritis, with similar complications and natural history.

Juvenile psoriatic arthritis occurs in two forms, one early-onset with a peak incidence around age 2 years, and a second form that occurs in later childhood or adolescence. The early onset form resembles oligoarticular JIA in several respects, including a propensity for asymmetric involvement of large joints, and association with ANA and uveitis, while later-onset disease typically presents with spondylarthritis and/or enthesitis, similar to adult-onset psoriatic arthritis. Dactylitis is characteristic of both forms of juvenile psoriatic arthritis [11].

Enthesitis-related arthritis (ERA) occurs mainly in boys older than 6 years of age, and is most often characterized by asymmetric arthritis involving the leg joints, including the hip. Although enthesitis, sacroiliac joint tenderness, and the presence of HLA-B27 antigen are associated with this disease, none is absolutely required for the diagnosis. ERA appears to represent a childhood-onset form of spondyloarthropathy [12]. In contrast to adult-onset spondyloarthropathy, disease is more likely to affect the hips and peripheral entheses, and less likely to affect the axial skeleton.

Systemic JIA (SJIA) affects males and females equally. In contrast to other forms of JIA, SJIA is a systemic illness with a strong auto-inflammatory component, characterized by prolonged fever, and markedly increased acute phase reactants including ferritin. Approximately 10% of cases of SJIA may be complicated by macrophage activation syndrome, a potentially life-threatening hemophagocytic disorder [13].

Criticism of the ILAR-2001 Classification

The 2001 ILAR classification has been criticized on several grounds. Regarding definitions for subgroups, ILAR-2001 relies heavily on physical findings of questionable relation to underlying disease mechanisms. Research into the pathophysiologic basis of different forms of JIA relies on the biologic uniformity of the patients under study. It now appears that some JIA subtypes, such as RF-negative polyarticular JIA and psoriatic JIA, comprise patients with heterogeneous disease mechanisms [11, 14]. On the other hand, some patients with pathophysiologically similar disease may fall into different categories. For example, a patient with spondyloarthropathy might be classified as either ERA, psoriatic arthritis, or undifferentiated arthritis, depending on their particular clinical features. Finally, there are discrepancies between how the same disease would be classified in a child as opposed to an adult patient.

To attempt to address some of these issues, the Pediatric Rheumatology International Trials Organization (PRINTO) has initiated a multi-year project to develop and validate an updated, evidence-based JIA-PRINTO classification [14]. In the initial stage of the project, a group of 13 expert pediatric rheumatologists participated in a web-based Delphi consensus survey, followed by a nominal group technique consensus conference. JIA was defined as chronic arthritis beginning before 18 years, as opposed to the age 16-year cutoff according to the ILAR-2001 definition. Moreover, the classification does not consider the number of joints involved. Provisional categories thus developed were published in 2019, and were limited to four defined categories: systemic JIA, RF positive JIA, enthesitis/spondylitis related JIA, early onset ANA-positive JIA. With the exception of early onset ANA-positive JIA, which appears to be a condition unique to childhood, these categories conform broadly to disease categories recognized in adults (Table 4.2). JIA that does not meet the definition for any of these categories is defined as "other." An international, large-scale project is currently underway with the goal of validating these criteria in a large cohort of at least 1000 new-onset children followed prospectively for at least 1–5 years. One shortcoming of the JIA-PRINTO provisional criteria is that a large proportion of patients remain unclassified: application of the criteria to data obtained from a large cohort of Canadian children within 6 months of diagnosis found that 63.3% of children were unclassifiable [15].

In addition, at a more fundamental level, there is a great deal of similarity between JIA and adult-onset forms of arthritis, both in terms of clinical presentation and genetic risk factors [16]. It has been argued that the overlap between adult and childhood-onset arthritis is so extensive that the concept of JIA as distinct, childhood-onset disease is an arbitrary distinction, and no longer a useful concept. Furthermore, consideration of pediatric and adult diseases as distinct entities has been an impediment to both basic and clinical research. At the regulatory level, this may result in unnecessary repetition of clinical studies before drugs proven to be useful in adult-onset forms of arthritis can be used in children with essentially the same conditions.

Table 4.2 PRINTO preliminary criteria for classification of JIA (2019)

Disease subtype	Clinical diagnostic criteria	Laboratory criteria
Systemic JIA	Fever of unknown origin daily (quotidian, rising to ≥39 °C once a day) for at least 3 consecutive days, and recurring over at least 2 weeks and accompanied by two major criteria, OR one major criterion and two minor criteria. Major criteria are 1. Evanescent rash 2. Arthritis Minor criteria are 1. Generalized lymphadenopathy, hepatomegaly, and/or splenomegaly 2. Serositis 3. Arthralgia lasting at least 2 weeks 4. Laboratory criterion	Leukocytosis (≥15,000) with neutrophilia
RF-positive JIA	Arthritis for at least 6 weeks, plus laboratory criterion	Association with two positive tests for RF at least 3 months apart, or at least one positive test for antibodies to cyclic citrullinated peptide (CCP)
Enthesitis/spondylitis-related JIA	Peripheral arthritis and enthesitis, OR Arthritis or enthesitis, plus ≥3 months of inflammatory lower back pain and sacroliitis on imaging, OR Arthritis or enthesitis, plus two of the following: 1. Sacroiliac joint tenderness 2. Inflammatory back pain 3. Laboratory criterion 4. Acute, symptomatic anterior uveitis 5. History of spondyloarthropathy in a first-degree relative	Presence of HLA-B27 antigen
Early-onset ANA-positive JIA	Arthritis for at least 6 weeks AND Onset at age 6 years or less AND Laboratory criterion	Presence of two positive ANA tests with a titer of ≥1:160 at least 3 months apart
Other JIA	Arthritis for ≥6 weeks, not meeting criteria for above disorders	
Unclassified JIA	Arthritis for ≥6 weeks, meeting criteria for ≥1 of above disorders	

Toward a Biologic Classification of JIA

During the past 40 years, there have been dramatic advances in the treatment of the different forms of JIA, with commensurate improvement in outcomes. However, JIA remains a group of diseases which in all of its forms is associated with increased risk for long-term effects on health and quality of life [17]. The goal of a possible biologic classification is to identify JIA subgroups defined by biologic mechanisms that can be targeted by specific and potentially more effective treatments.

Recently, a group of investigators engaged in mechanistic JIA research proposed a “road map to a molecular nomenclature” for research toward more precisely defining biologic subgroups of JIA, based on large-scale collaborative studies, and incorporating methods including genomic strategies, cell profiling, autoantibody arrays, proteomics, lipidomics, and advanced histological methods [18]. Although JIA is clearly not exclusively a genetic disease, studies employing genomic sequencing, with functional validation of genetic variants, may be particularly informative. Research toward a biologic classification of JIA is likely to become a self-reinforcing process; identification of disease-specific genetic factors and biomarkers may facilitate subsequent studies on increasingly homogeneous patient populations. This approach has the potential to resolve some of the controversy surrounding the classification of childhood arthritis in the foreseeable future.

Treatment of JIA

With timely diagnosis and initiation of effective anti-inflammatory therapy, disease remission can be achieved in the great majority of children with JIA. For children with oligoarticular disease, injection of long-acting corticosteroids into affected joints may produce local remission lasting several months or longer. Pharmacotherapy of the polyartic-

Table 4.3 Pharmacologic treatment of selected JIA subtypes

	Systemic JIA without MAS	Systemic JIA with MAS	Oligoarticular JIA	Polyarticular JIA	Enthesitis-related JIA
First line treatment	NSAID	IL-1 or IL-6 antagonist with CS	Intra-articular CS (triamcinolone hexacetonide preferred) Adjunctive treatment: short course NSAID	Methotrexate Adjunctive treatment: bridging treatment with systemic CS for <3 months	NSAID
Second line treatment	IL-1 or IL-6 antagonist	Calcineurin inhibitor	Methotrexate	Biologic DMARD (TNF inhibitor, abatacept, or tocilizumab)	TNF inhibitor
Third line treatment	Add CS for persistent systemic disease, minimize dose and duration MTX and/or biologic DMARD for persistent joint disease		Biologic DMARD (TNF inhibitor, abatacept, or tocilizumab)	Change biologic DMARD Switching class of medication preferred over increase dose for moderate to severe disease	Sulfasalazine or MTX may be used for patients intolerant of biologic medications
Additional/ experimental pharmacologic treatments		Emapulamab IVIG JAKi Plasmapheresis Cytotoxic agents		JAKi Rituximab	IL-17 antagonists IL-23 antagonists JAKi

MAS—macrophage activation syndrome, NSAID—non-steroidal anti-inflammatory drug, CS—corticosteroids, MTX—methotrexate, TNFi—tumor necroses factor inhibitor, IL—interleukin, JAKi—Janus kinase inhibitor, IVIG—intravenous immunoglobulin. First-, second-, and third-line treatment recommendations are based on American College of Rheumatology guidelines [19, 20]. Many of the medications listed under "additional/experimental pharmacologic treatments" have not received regulatory approval for treatment of JIA. Physicians should consult current local regulations before prescribing any of these drugs

ular forms of JIA is similar to treatments used for adult-onset forms of arthritis. Short-term treatment with non-steroidal anti-inflammatory drugs and methotrexate may be used initially. An increasing number of cytokine antagonists, and immunomodulators including Janus kinase inhibitors, are available for use in cases of refractory disease. Drug selection may be influenced by disease subtype (Table 4.3). Despite advances in treatment, the long-term prognosis for children with JIA remains guarded. Even the best, subtype-specific biologic treatments remain expensive, have potential side effects, and usually need to be given for a long time to achieve optimal effects. Disease remains active into adulthood in about half of the patients [18]. Progress toward the development of a biologically based classification for childhood-onset chronic arthritis is expected to aid in the development of improved therapies tailored to specific disease subtypes.

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5

Adult-Onset Still's Disease (AOSD)

Maria Kourilovitch and Claudio Galarza-Maldonado

Abstract

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder of polygenic origin, which is based on pathologic immune mechanisms due to the complex interaction of genetic and environmental factors. AOSD can occur sporadically in all adult age groups and is characterized by a potentially severe inflammatory onset accompanied by a wide range of symptoms and complications. Diagnosing and treating AOSD consistently presents a challenge, primarily due to the need for comprehensive clinical guidelines.

Keywords

Adult-onset Still's disease · Arthritis · Fever · Ferritin

Introduction

Adult-onset Still's disease (AOSD) stands as a rare systemic autoinflammatory disease characterized by febrile fever, arthritis, skin rash, and elevated ferritin levels that bear similarities to systemic juvenile idiopathic arthritis. The historical backdrop of AOSD traces back to Bywaters in 1971, who documented the clinical characteristics of 14 adult patients that mirrored those of Still's disease. The reason underlying the nomenclature of this disease is that AOSD is similar to certain symptoms of pediatric Still's disease, which is currently classified as systemic juvenile idiopathic arthritis (SJIA). Based on gene expression analysis, it is believed that the pediatric and adult variants of Still's disease are a single nosologic entity [1]. AOSD is classified as an orphan disease with annual incidence of 0.16–0.62 cases per 100,000 individuals. However, there is a markedly increased incidence in individuals after SARS-Cov2 infection (0.75 per 100,000 people), COVID-19 vaccination (0.81 per 100,000 people) or both, SARS-Cov2 infection + COVID-19 vaccination (1.69 per 100,000 people) [2]. It is important to note that the incidence and prevalence of AOSD have increased over the past 20 years compared to that reported before 2000. This increase is largely due to the heightened awareness of the medical community about the disease [3]. According to recent data, AOSD more often develops in women than in men [3] and usually manifests in middle-aged individuals; however, AOSD in the elderly, although less common but gradually increased in recent years. This trend is currently an area of special interest due to some peculiarities of clinical manifestations and the elevated risk of complications [4].

Many factors have been postulated to play a role in the development of this disease. These include genetics (linked to human leukocyte antigen [HLA] DRB1*1201 and 1501, B35, DR2, and DR5), infections (both viral and bacterial), and an imbalanced immune system characterized by dysregulated activation of macrophages and neutrophils in response to a danger signal, leading to a cytokine storm. In addition, it has been suggested that stressful life events related to work, family, and health may serve as potential triggers for AOSD [4].

It has been suggested that AOSD, together with macrophage activation syndrome, catastrophic antiphospholipid syndrome, and septic shock, which have similar clinical and laboratory features and are characterized by excessive elevation of serum ferritin levels, could potentially be subsumed under a collective term called "hyperferritinemic syndrome". Recent evidence has suggested an association between ferritin levels and progression to life-threatening conditions in individuals with systemic lupus erythematosus, polydermatomyositis, severe COVID-19, and multisystem inflammatory syndrome [5].

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Clinical Manifestations

As an autoinflammatory disease, AOSD has several key features, including intense inflammation with periodic fever, tissue inflammation depending on the specific disease manifestations, increased leukocyte and neutrophil counts, and elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels.

AOSD manifests with four primary symptoms: fever, rash, arthralgia and/or arthritis, along with elevated leukocytes (more than 10,000), and neutrophils (more than 80%). Various other symptoms may also be associated with the main symptoms (Table 5.1 [4]).

Fever is one of the most critical symptoms in active AOSD and can reach high temperatures, appearing suddenly and disappearing without antipyretics. Typically, the fever occurs daily in the evenings, and there may be double peaks during the day and evening. For many AOSD patients, the fever is intermittent, but it is remittent in up to 20%. In some cases, fever may be the only symptom of AOSD. Therefore, AOSD is the definitive diagnosis in up to 20% of cases of fevers of unknown origin. It is important to remember that in the case of an established disease, the patients with AOSD may present with symptoms of residual inflammation and no fever.

A characteristic rash, histologically a non-specific superficial perivascular dermatitis, often appears with the rise in body temperature and disappears suddenly, similar to the fever. The rash in Adult-onset Still's disease is typically macular or maculopapular with a distinct "salmon" color. Koebner's phenomenon is characteristic of Still's rash because of its rapid onset in areas of clothing contact. The rash is commonly found on the skin of the extremities, trunk and neck, and rarely involves the face, palms, or soles [6]. An atypical rash, histologically an interface dermatitis, is significantly more common in older patients [7].

Arthralgias and arthritis are prevalent in Adult-onset Still's disease, affecting the small joints in the hands, wrists, elbows, ankles, knees, and sacroiliac joints. Initially, arthritis is typically mild and localized, but as the disease progresses, it becomes more severe and widespread. A characteristic phenomenon of AOSD is the development of joint narrowing and erosions after approximately 6 months of disease, with a progression to carpal ankylosis, in subsequent years [8]. This occurs without structural damage of metacarpophalangeal or proximal interphalangeal joints, in contrast to RA [7], and the cause of which is not fully understood. Some patients also experience ankylosis in their feet and cervical spine. Synovial biopsy of inflamed joints shows nonspecific synovitis, and synovial fluids present high cellularity.

Table 5.1 Clinical manifestations of AOSD patients among the largest published series 2015–2020 years

Clinical manifestation	Frequency range (%)
Fever >39.0 °C	91.3–100
Arthralgia	47.2–94.9
Arthritis	50.7–64.6
Typical rash	62.2–79.9
Sore throat	31.8–63.5
Lymphadenopathy	28.1–60.4
Splenomegaly	25.0–60.4
Pericarditis	3.1–17.3
Myalgia	25.6–52.8

In some cases, general symptoms become prominent and significantly affect patients. In more than 70% of cases, the disease process begins with a throat inflammation resembling a sore throat. Myalgia is also a commonly observed symptom in patients with AOSD. Lymphadenopathy, hepatomegaly, and splenomegaly are common manifestations during the initial phases of the disease, indicating tissue infiltration by cells associated with inflammation and heightened immune activity of the reticuloendothelial system. These symptoms are often accompanied by abdominal pain, which also lacks clear cause. Lymphadenopathy is observed in 65% of patients but rarely emerges as a dominant clinical feature.

Laboratory Findings

A standard laboratory panel for a patient with AOSD often includes leukocytosis with neutrophilia, elevated acute phase reactants including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and markedly elevated ferritin levels (Table 5.2 [4]).

The serum ferritin level in AOSD is higher than in other autoimmune, infectious, or neoplastic diseases, while glycosylated ferritin is low (<20%). Although not specific, these findings also occur in severe systemic infection and hemophagocytic syndromes. A glycosylated ferritin level below 20% appears to be a better diagnostic marker of AOSD than an elevated level of serum ferritin, and the combination of both abnormalities may be beneficial in the differential diagnosis of AOSD. The specificity of ferritin levels above the upper limit of normal less than ×5 UNL (35.8%) is too low to be clinically useful. However, the combination of elevated ferritin and glycosylated ferritin less than 20% has a specificity of 83%, and the combination of elevated ferritin greater than ×5 UNL and glycosylated ferritin less than 20% has a specificity of 92.9% [9]. On the other hand, the combination of hyperferritinemia with Yamaguchi criteria, using ferritin levels from ≥750 mg/L to ≥2500 mg/L provides a specificity of 98.8% and 99.9%, respectively [10].

Table 5.2 Laboratory and serological findings in AOSD patients among the largest published series 2015–2020 years

Laboratory findings	Frequency range(%)
Leukocytosis (>10,000/mL)	23.6–96.8
Leukocytosis (>15,000/mL)	31.7–93.5
Neutrophils (>80%)	32.0–98
Anemia <10 g/dL	13–74.5
Thrombocytopenia (platelets $<15 \times 10^4$)	0–13.6
Thrombocytosis (platelets >40,000/mm^3)	37.6–46
Elevated ESR	68.9–98.2
Elevated CRP	91.5–98.2
Hyperferritinemia	56.4–96.7
Serum ferritin >3000 ng/mL	60–81.1
Glycosylated ferritin (≤20%)	72.2–79.5
Abnormal liver function/raised ALT and/or AST	50.4–61.6
Hypoalbuminemia (albumin ≤3.5 g/dL)	41–72
Raised LDH	69.0–81.5
ANA positive	2.9–25.8
RF positive	0–20.1

ANA antinuclear antibody, *AOSD* adult-onset Still's disease, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *LDH* lactate dehydrogenase, *RF* rheumatoid factor

Neutrophil to lymphocyte ratio (NLR) ≥4 has been proposed as an easily accessible biomarker in AOSD patients, with a sensitivity of 93.8% and specificity of 61.7%. Using NLR as a main criterion with the Yamaguchi or Fautrel classification improves its sensitivity [11].

In particular, some case series have reported rheumatoid factor (RF), with a small proportion of patients having positive RF and ANA. Although AOSD is considered a seronegative disease according to the Yamaguchi criteria, it should still be considered in seropositive patients with a typical clinical presentation and other compatible findings.

However, recent advances emphasize the important role of pro-inflammatory cytokines such as interleukin IL-1, IL-6, IL-18 and IL-37, TNF, interferon and other biomarkers in diagnosing and managing AOSD. The pro-inflammatory cytokines are associated with clinical symptoms; for istance, fever is associated to IL-1, arthritis and typical skin rash to IL-6, and IL-18 to hemophagocytic syndrome and liver damage.

The serum level of IL-6 is significantly lower in patients with elderly onset compared to those with middle-aged onset. In contrast, IL-18, CRP, and ferritin levels do not show any significant difference between these groups.

All cytokines detected in AOSD are involved in the regulation of ferritin synthesis, with their levels positively correlated with ferritin levels and disease activity. High serum levels of IL-1, IL-6, and IL-18 are detected in systemic forms of AOSD and could be used as biomarkers of disease activity.

Procalcitonin, a marker of severe systemic infection, may be elevated in patients with active AOSD and, therefore, cannot be used for differential diagnosis.

Radiographic Findings

Initial radiographs at the onset of AOSD may appear nonspecific. A characteristic feature of AOSD is diffuse radiocarpal, intercarpal, and carpometacarpal joint space narrowing without productive bony changes. Joint space narrowing is uniform, and bony erosions may also be observed. In the late stages of the disease, C carpal ankylosis and sometimes ankylosis of the feet and spine may occur.

Synovitis is the most common MRI finding, seen in 60.5%, primarily in peripheral joints. It presents with low to intermediate signal intensity on T1-weighted images and intermediate to high signal intensity on T2-fat-saturated weighted and STIR images. Bone edema and MRI bone erosions are reported on 34.9% and 25.6% of MRI scans, respectively. Patients with MRI bone erosions tend to have a higher prevalence of splenomegaly, a more chronic disease course, and lower erythrocyte sedimentation rate and ferritin levels [12].

In cases of AOSD with systemic manifestations, CT may reveal axillary and mediastinal lymphadenopathies, pleural and pericardial effusions, and infiltrates in both lung bases [13].

Course and Disease Patterns

The course of AOSD can be broadly categorized into three patterns, which have important implications for prognosis and management: a self-limiting form, an intermittent form with recurrent flares, and a chronic form characterized by persistent disease activity.

Traditionally, patients with AOSD have three primary disease patterns: monocyclic, polycyclic, and chronic articular.

The monocyclic pattern is a single systemic episode that resolves completely within a few months.

The polycyclic (or intermittent) pattern involves one or more flares interspersed with complete remissions that may last several years.

Conversely, the chronic articular pattern typically presents as persistent polyarthritis.

Persistently elevated ferritin levels after effective treatment may indicate a progressive chronic joint course. Additionally, a large multicenter study showed that a prolonged diagnostic process significantly correlates with the onset of chronic disease. Specifically, relapses or chronic joint patterns were more frequent when diagnosis was delayed by more than six months [14].

Diagnosis and Classification Criteria

Yamaguchi [15] and Fautrel [16] criteria (Table 5.3) are the most commonly used classification criteria for AOSD. Both criteria show good sensitivity and specificity. However, a disadvantage of the Yamaguchi criteria is the lack of clear parameters in the exclusion criteria, which may lead to difficulties in interpretation. This absence of well-defined exclusion criteria is a particularly sensitive parameter when performing retrospective studies or analyses in groups of patients with this pathology when clinical information confirming the exclusion pathology may not be available. The requirement of negativity for ANA and RF without specifying the level of these parameters may also cause difficulties or confusion in the classification of AOSD when these markers are present in low titers. Moreover, in daily clinical practice, performing all the necessary tests to exclude all the pathologies described in the exclusion criteria is virtually impossible. At the same time, the modified Yamaguchi criteria, which include parameters for the levels of hyperferritinemia and glycosylated ferritin, can increase its specificity to almost 100% [17].

Table 5.3 Most commonly used classification criteria for AOSD

Yamaguchi et al. classification criteria for AOSD	Fautrel et al. classification criteria for AOSD
Major criteria: 1. Fever ≥39 °C lasting at least 1 week 2. Arthralgia or arthritis for ≥2 weeks 3. Typical nonpruritic salmon-pink skin rash 4. Leukocytosis ≥10,000/mm^3 with ≥80% polymorphonuclear cells	Major criteria: 1. Spiking fever ≥39 °C 2. Arthralgia 3. Transient erythema 4. Pharyngitis 5. Polymorphonuclear cells ≥80% 6. Glycosylated ferritin ≤20%
Minor criteria: 1. Sore throat 2. Lymph node enlargement 3. Hepatomegaly or splenomegaly 4. Abnormal liver function tests 5. Negative ANA and RF tests Exclusion criteria: 1. Infections (especially, sepsis and infectious mononucleosis) 2. Malignancy (mainly malignant lymphoma) 3. Other rheumatic disorders (mainly polyarteritis nodosa and rheumatoid vasculitis with extraarticular features)	Minor criteria: 1. Maculopapular rash 2. Leukocytes ≥10,000/mm^3
For diagnosis of AOSD, the patient should meet 5 or more criteria, of which at least 2 should be major	For diagnosis of AOSD, the patient should meet 4 or more major criteria OR 3 major criteria + 2 minor criteria
Sensitivity 96.3%, specificity 98.2%, PPV 94.6% and NPV 99.3% Modified Yamaguchi criteria, i.e., Yamaguchi criteria and ferritin >ULN: sensitivity 100%, specificity 97.1%, PPV 87.1%, and NPV 100% Alternative modified Yamaguchi criteria, i.e., Yamaguchi criteria and glycosylated ferritin ≤20%: sensitivity 98.2%, specificity 98.6%, PPV 93.0% and NPV 99.6%	Sensitivity 87.0%, specificity 97.8%, PPV 88.7%, and NPV 97.5%

ANA antinuclear antibody, *AOSD* adult-onset Still's disease, *RF* rheumatoid factor

The Fautrel classification criteria for Adult-onset Still's disease do not require exclusion criteria to be met and do not set a time frame for symptoms, allowing for earlier classification of the disease. Low glycosylated ferritin is also a more sensitive marker of AOSD than serum ferritin. However, a disadvantage of this parameter is that its availability in medical centers is still limited.

Differential Diagnosis of AOSD

Between 10% and 20% of cases of fever of unknown origin (FUO) are subsequently classified as AOSD. The clinical scale proposed by Crispin et al. facilitate differential diagnosis at an early stage of the disease and has a high specificity of up to 98% [18] (Table 5.4).

In the differential diagnosis of Adult-onset Still's disease, this other patologies to consider include [7]:

- Infectious diseases: pyogenic bacterial septicemia, infectious endocarditis, biliary, colic or urinary occult infections, tuberculosis, brucellosis, and yersiniosis; HIV infection, viral hepatitis, parvovirus B19 infection, herpesvirus infections, measles, rubella and COVID 19; toxoplasmosis and abscessed parasitosis;
- Malignant diseases: Hodgkin disease or non-Hodgkin lymphoma, angioimmunoblastic lymphadenopathy, Castleman disease and myeloproliferative disorders; kidney, colon or lung cancer and paraneoplastic syndromes;
- Systemic autoimmune and autoinflammatory disease: systemic lupus erythematosus, polymyositis, dermatomyositis, rheumatoid arthritis, polyarteritis nodosa or other vasculitis, hereditary autoinflammatory syndromes: familial Mediterranean fever, mevalonate kinase deficiency, TNF receptor-associated periodic syndrome and cryopyrin-associated periodic syndromes; neutrophilic dermatosis and Sweet syndrome; post-streptococcal arthritis, reactive arthritis, sarcoidosis, Schnitzler syndrome, Kikuchi-Fujimoto disease and drug-related hypersensitivity.

Table 5.4 Clinical scale for diagnosis of AOSD in setting of FUO by Crispin et al. [18]

Criterion	Description	Points
Arthritis	Presence of synovitis	10
Pharyngitis	Present at the beginning of the disease	7
Still's rash	Macular or maculopapular pink-salmon rash that accompanies the fever	5
Splenomegaly	Detected clinically or by imaging studies (>11 cm)	5
Neutrophilia	Total neutrophil count higher than 9.5 × 10^3/mL	18
Total		45

If a patient with FUO has ≥30 points, the diagnosis of AOSD can be established without further diagnostic workup, with a high specificity (~98%)
AOSD adult-onset Still's disease, *FUO* fever of unknown origin

Treatment of AOSD

The classic first-line treatment of AOSD after diagnosis is the administration of NSAIDs, glucocorticoids (GS) (either as pulse therapy or orally at 1 mg/kg), and methotrexate. In practice, however, about 30–40% of patients only partially respond to this treatment. Although this recommendation remains in the treatment guidelines of different countries, experts are insisting on the early use of modern targeted biological treatment. Currently, the IL-1 inhibitors canakinumab and anakinra are approved for the treatment of AOSD in Europe, while only canakinumab is approved in the USA. When used as a first-line biological therapy for AOSD, canakinumab has shown rapid and pronounced results, often culminating in complete clinical remissions. Early administration of IL-1-blocking therapies correlates with improved disease prognosis and superior retention rates [19].

Rilonacept, tumor necrosis factor-alpha (TNF-α) blockers, and tocilizumab are employed off-label. The TNF-α blockers often result in partial responses, but they may benefit patients with arthritis without systemic symptoms.

The latest EULAR/PReS (2024) guidance emphasizes minimizing prolonged glucocorticoid use by prioritizing IL-1 and IL-6 inhibitors, advocating for their initiation upon diagnosis. The treatment algorithm addresses high disease activity and recommends high-dose GC for severe cases, with tapering once intermediate targets are met. Experimental therapies, including JAK inhibitors, may be considered for specific disease features. Remission is defined as clinically inactive disease maintained for six months, with tapering of therapies based on injection spacing. Patient education is crucial for recognizing relapse signs and maintaining communication with healthcare providers [20].

Other biologic agents, including tocilizumab, abatacept, rituximab, and targeted synthetic tofacitinib, have been studied to treat AOSD. Tocilizumab may serve as an alternative to IL-1 antagonists, particularly in cases with severe joint involvement. Abatacept, a T-lymphocyte activation modulator, and rituximab, an anti-CD20 monoclonal antibody have been studied in treatment-resistant AOSD patients with minimal benefit. A recent case study suggested that the Janus kinase (JAK) inhibitor tofacitinib, when used in refractory AOSD patients, may lead to disease remission and a reduction in corticosteroid dosage, particularly in cases of polyarthritis [4].

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Systemic Sclerosis

6

Gema Maria Lledó and Gerard Espinosa

Abstract

Systemic sclerosis (SSc), also known as scleroderma, is a chronic orphan disease of an unknown etiology, characterized by autoimmunity mediated through specific autoantibodies and auto-reactive T cells. It is hallmarked by dermal and visceral fibrosis, alongside a concurrent vasculopathy terrain reminiscent of Raynaud's phenomenon, pulmonary arterial hypertension, and less commonly, scleroderma renal crisis. Despite its relatively low prevalence, the disease exerts a substantial burden. Recent milestones, including the 2013 ACR/EULAR classification criteria, coupled with a diverse array of reviews and research advancements, have notably enhanced our insights into its pathogenesis and clinical manifestations, expanding our therapeutic armamentarium. The paramount significance of early and precise diagnosis is underscored, harmonized with ongoing endeavors to stratify patient risks. This serves as a crucial element in predicting both organ involvement and the course of disease progression. Considering the heterogeneous expression of the disease, a comprehensive evaluation of the patient becomes imperative. This encompasses the selection of a therapeutic approach that not only attains therapeutic efficacy but also minimizes associated adverse effects. Crafting the most effective therapeutic strategy demands a holistic approach, meticulously calibrating therapeutic impact against potential side effects, all the while aligning interventions with the specific care goals of the patient.

Keywords

Systemic sclerosis · Scleroderma · Classification criteria · Autoantibodies · Fibrosis · Vasculopathy

Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease characterized by endothelial dysfunction, fibrosis, and the production of autoantibodies (AAs). Excessive collagen deposition results in skin thickening and changes in internal organs that include the lung, vasculature, gastrointestinal tract, and kidney. Endothelial damage leading to vascular dysfunction manifests as Raynaud's phenomenon, digital ulceration and gangrene, pulmonary arterial hypertension (PAH), and renal vascular damage. SSc is usually subclassified as limited (lcSSc) or diffuse (dcSSc) depending on the extent of skin involvement. The distinction between limited and diffuse SSc varies, but most authorities define dcSSc as skin thickening proximal to the elbows and knees (upper arms, thighs or trunk, the latter including the anterior chest, abdomen, and back) documented at any time during the illness, according to first criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee [1]. In contrast, lcSSc includes SSc patients with either limited (restricted to the fingers, hands, and/or forearms) skin thickness or no skin thickness (SSc sine scleroderma). Skin thickening affecting the face can be present in either dcSSc or lcSSc and its detection or absence does not alter the subtype classification. Typically, patients with limited SSc have a more insidious disease onset, and they describe Raynaud's phenomenon for some years prior to the onset of sclerodactyly. In contrast, in those with diffuse SSc the skin thickening tends to more closely coincide with the onset of Raynaud's phenomenon and the disease course is more acute, with most internal organ involvement occurring within 5 years.

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Epidemiology

Incidence and Prevalence

A study conducted by Zhong et al. [2] analyzed the global incidence and prevalence patterns of SSc across different regions. Prevalence rates were higher in European populations (ranging from 10 to 35 per 100,000) compared to East Asian populations (ranging from 3.8 to 5.6 per 100,000) and South American populations (29.6 per 100,000). Notably, the indigenous people of Canada exhibited the highest prevalence (47 per 100,000). The pooled prevalence rate was calculated to be 23 per 100,000. Regarding ethnicity, African-American individuals with SSc may experience an earlier onset and increased mortality, but also socioeconomic status could hold even greater predictive value for mortality in this patient subgroup.

Age

Systemic sclerosis predominantly emerges during middle age, and the age of onset has an impact on disease severity. In a study by Carreira et al. [3], early SSc patients were classified into distinct age groups, revealing that younger patients exhibited higher levels of anti-Scl-70 antibodies and a greater likelihood of developing dcSSc. On the other hand, older patients were more prone to lcSSc and demonstrated an increased frequency of cardiac involvement.

Gender Differences

A review by Hughes et al. [4] highlighted gender disparities in SSc. While females predominate (with a female-to-male ratio of 3:1–7:1), males tend to exhibit a preference for dcSSc, whereas females tend to present with lcSSc. These gender variations also extend to disease severity, organ involvement, and the prevalence of complications such as PAH. In fact, estrogens, especially estradiol, have been demonstrated to influence the progression of SSc, potentially exerting profibrotic effects and influencing the emergence of PAH.

Environmental and Occupational Exposures

Occupational exposure to specific substances, such as silica and organic solvents like aromatic or chlorinated compounds, has been linked to SSc. Moreover, exposure to heavy metals like antimony, cadmium, lead, and mercury has also been associated with SSc, with varying gender-specific associations.

Genetics

The relative risk of developing SSc, if a first-degree relative has it, is a remarkable 13%, although the absolute risk in individual family members is much lower at <1%. Recent genome-wide association studies (GWAS) have unveiled associated genetic variants predominantly situated in non-coding genomic regions. These variations exert their influence primarily on the immune system of SSc patients. Notably, these genetic aberrations manifest in several key aspects of immune functionality. Within innate immunity, genes such as IRF5, IRF7, and TLR2 demonstrate variations. Genetic deviations in genes related to T- and B-cell activation, such as CD247, TNFAIP3, STAT4, and BLK, have been identified, corroborating earlier findings. Furthermore, alterations in genes pertinent to the NF-kB pathway, including TNFAIP3 and TNIP1, are prevalent in SSc patients, aligning with existing biological insights. Beyond their immune-related roles, certain genes like CSK, DDX6, DNASE1L3, and GSDMA/B also exhibit potential involvement in the vascular and fibrotic components of SSc [5].

Type 1 interferons (T1 IFNs), essential cytokines in viral response and immune activation, seem to be implicated in SSc [6]. Detecting T1 IFN levels directly in humans is complex, leading to the adoption of an “interferon signature” measured through interferon-stimulated gene (ISG) expression. An early IFN signature in monocytes has been found in initial SSc stages, preceding fibrosis, implicating it in early pathogenesis. Elevated IFN signatures in SSc blood correlate with specific antibody profiles, particularly anti-topoisomerase I and anti-U1-RNP antibodies, highlighting the link between IFN signaling and autoimmunity.

Laboratory Findings

Numerous potential biomarkers have been extensively studied in SSc, and a few have emerged as feasible candidates for clinical assessment. Among these accessible biomarkers, elevated levels of C-reactive protein (CRP) have been observed in a subgroup of SSc patients, linked to heightened risks of progressive fibrosis and mortality [7]. The upregulation of CRP is driven by interleukin (IL)-6, and IL-6 serum concentrations correlate with unfavorable disease trajectories in individuals with interstitial lung disease. CRP and IL-6 have been employed in stratifying patients for clinical studies, thus holding significance in translating research into clinical practice [8]. Additionally, serum biomarkers such as Krebs von den Lungen glycoprotein-6 (KL-6) and chemokine ligand 18 (IL-18) have shown predictive potential for assessing interstitial lung disease severity and progression [9]. These baseline elevations, along with their persistence despite treatment, could offer valuable guidance in therapeutic decision-making. N-terminal pro-B-type natriuretic peptide stands as a valid early biomarker for PAH, often complementing other disease characteristics to determine the need for right-heart catheterization.

Antinuclear Antibodies

In SSc, circulating antinuclear antibodies hold diagnostic significance and can be detected in 90–95% of patients through methods like immunofluorescence, enzyme-linked immunosorbent assay, immunodiffusion and immunoblotting. Numerous autoantibodies have been described, but less than 15 are clinically used and only 3, namely autoantibodies that target topoisomerase I (TOPO-I or Scl-70), centromere proteins (ACA) and RNA polymerase III (RNAP-3), were included in the classification criteria for SSc. Other autoantibodies have been reported in SSc including those targeting the ribonuclear proteins (anti-U11/U12 RNP, anti-U1 RNP, and anti-U3 RNP) and nucleolar antigens (anti-Th/To, anti-NOR 90, anti-Ku, antiRuvBL1/2, and anti-PM/Scl) [10] (Table 6.1).

Different antibodies are associated with distinct clinical features, offering insights into organ involvement and prognosis. Respect to the three most common AAs, anti-Scl-70 correlates with severe cutaneous and internal organ fibrosis, ACA with limited skin fibrosis and complications like PAH and anti-RNAP-3 with rapid skin thickening, renal crisis, and malignancy risk. Less common, anti-U3 RNP and anti-U11/U12 RNP relate with severe lung disease, and anti-U1 RNP with muscle and joint inflammation. Moreover, anti-Th/To antibodies indicate lung involvement and inflammatory muscle disease, while anti-NOR 90 antibodies associate with limited cutaneous involvement and mild internal organ fibrosis. Anti-PM/Scl and anti-Ku antibodies are tied to muscle, joint, and overlap disease involvement. Anti-RuvBL1/2 is linked to diffuse cutaneous fibrosis and myositis overlap. Finally, anti-eIF2B, cytoplasmic SSc-specific autoantibodies detected in ANA-negative sera, is marked by both dcSSc and interstitial lung disease. The absence of

Table 6.1 Prevalence, pattern, skin subset, and organ involvement associated with SSc-specific antibodies. Adapted from the article by Stochmal et al. [10]

Antinuclear antibodies	IIF pattern ICAP	Prevalence (%)	Cutaneous subset	Organ involvement and associated diseases
Anti-Scl70	Speckled (AC-29)	9.4–42	Diffuse	Interstitial lung disease, renal crisis, digital ulcers early in the disease
Anti-centromere	Centromere (AC-3)	20–40	Limited	Pulmonary arterial hypertension, digital ulcers late in the disease
Anti-RNAP-3	Speckled (+/− nucleolar) (AC-10)	11	Diffuse	High risk of malignancy, renal crisis, gastric antral vascular ectasia
Anti-U3 RNP fibrillarin	Nucleolar (AC-9)	4–10	Diffuse/limited	Interstitial lung disease, pulmonary hypertension, renal crisis, myocardial fibrosis, gastro-intestinal involvement, myositis
Anti-U1 RNP	Speckled (AC-5)	6–7	Limited	Mixed connective tissue disease, arthritis, myositis
Anti Th/To	Nucleolar (AC-8)	2–5	Limited	Interstitial lung disease, pulmonary hypertension, myositis
Anti-NOR 90	Nucleolar (AC-10)	4.8	Limited	Mild involvement of internal organs. Could be found in other autoimmune diseases such as rheumatoid arthritis, SLE, and Sjögren's syndrome
Anti-U11/U12 RNP (RNPC-3)	Speckled (AC-4, AC-5)	3	Diffuse/limited	Interstitial lung disease, pulmonary hypertension
Anti-PmScl	Nucleolar (AC-8)	2	Limited	Myositis overlap
Anti-Ku	Speckled (AC-4)	1.5–5	Limited	Myositis, arthritis
Anti-RuvBL 1/2	Speckled	1–2	Diffuse	Myositis
Anti-eIF2B	Speckled-cytoplasmic	1	Diffuse	Interstitial lung disease

AC anti-cell, *IIF* indirect immunofluorescence, *ICAP* International Consensus on Autoantibody Patters (www.anapatterns.org) serum ANA does not exclude the diagnosis of SSc. A certain group of patients (5–9%) is ANA negative and generally has a distinct subtype of the disease, with less vasculopathy, a greater proportion of men, more frequent lower gastrointestinal involvement, and a more severe disease course. Importantly, anti-Th/To are the most common antibodies in patients who tested ANA negative with widely available commercial assays (a false negative group of patients). Conversely, the concurrent presence of anti-Scl-70, ACA, or RNAP-3 is exceedingly uncommon (1%). Therefore, meticulous confirmation of positivity through specialized immunological assays is of paramount significance to corroborate such cases.

Systemic Manifestations and Comprehensive Overview of Primary Treatment Approaches

Systemic sclerosis exhibits highly heterogeneous clinical phenotypes among patients, with its variability being influenced not only by the extent of cutaneous involvement that defines distinct disease subtypes, but also by the specific autoantibody profile and its association with heightened susceptibility to specific complications. The most frequent clinical manifestations, their respective prevalence rates, established risk factors, diagnostic methodologies, and therapeutic modalities are comprehensively outlined in Table 6.2 [11, 12].

Table 6.2 Overview of systemic manifestations and treatment in systemic sclerosis [Adapted from the articles 11–12]

Organ system affected	Complications	Prevalence	Clinical features	Risk factors	Screening and monitoring	Treatment
Raynaud's phenomenon (RP)	Digital ulcers (DU)	RP (>90%) DU (~50%)	RP: triphasic color change: initial pallor (vasospasm), blue/purple (cyanosis) and erythema (hyperemia)	DU: ACA > Scl-70/ RNAP3	Clinical evaluation	Nitroglycerine, CCB, PDE5-I, ERA, prostacyclin analogs, digital sympathectomy, botulinum toxin
Skin and Mucosa	Skin fibrosis	Depends on SSc subset	Diffuse skin fibrosis Sclerodactyly Orofacial (microstomia and sclerosis of eccrine glands resulting in sicca syndrome) Skin overlying joints leads to friction rubs, contractures, and joint deformities	Scl-70, anti-RNAP3 ≫ACA	Clinical evaluation mRSS Skin ultrasonography	MTX, MMF, RTX, CPM, TCZ, AHSCT
	Calcinosis	20–40%	Occurs at fingertips and over extensor surfaces. May be asymptomatic or cause pain and ulceration. Risk of infection	ACA (including lcSSc subtype)	X-ray images Skin ultrasonography	Surgical excision (most effective) Others: topical/ intravenous sodium thiosulfate, JAK-inhibitors (variable response)
Musculoskeletal	Join involvement	24–80%	Arthralgia, synovitis, contracture, and TFRs may be present	Scl-70, U1-RNP, PmScl, Ku	X-ray images Join ultrasonography	MTX, HCQ, RTX, TCZ
	Myalgia, myositis	23–60%	Symmetrical and proximal muscle pain and weakness in both upper and lower limbs	PmScl, Ku, Scl-70, Th/To, RNA-P3, U1-RNP	EMG, whole-body MRI	MTX, MMF, RTX

(continued)

Table 6.2 (continued)

Organ system affected	Complications	Prevalence	Clinical features	Risk factors	Screening and monitoring	Treatment
Respiratory	ILD	30–52.3% (usually within the first 5 years)	Dyspnea, decreased exercise tolerance, chronic cough, basal lung crackles	dcSSc, ATA, male sex	Basal HRCT. PFT (FVC, diffusion)/4–6 months during first 3 years	MMF, CPM, RTX, TCZ, AHSCT, nintedanib, pirfenidone, pulmonary transplant
	PAH	5–12%	Asymptomatic (early), later: dyspnea, decreased exercise tolerance	Older age, late-onset, digital ulcers, numerous telangiectasia	DETECT[a] PFT Right heart catheterization to confirm diagnosis	CCB, PDE5-I, ERA, prostacyclin analogues, riociguat
Cardiac	Heart failure Pericardial effusion Arrhythmias	7–32%	Dyspnea, decreased exercise tolerance, chest pain, palpitations, syncope, fatigue, dizziness, peripheral edema	Scl-70, older age	Annual echocardiogram, ECG, TnI, BNP. Cardiac MRI if high risk	Loop diuretics, CCB Colchicine, HCQ, MMF, MTX, CPM (avoid BB for risk of aggravating RP)
Renal	SRC	2–15% (usually first 5 years)	Hypertension, pulmonary and peripheral edema, renal dysfunction, uremia, proteinuria	Male sex, anti-RNAP3, dcSSc, older age, systemic CS (>15 mg PDN/day)	Measure creatinine clearance, urea, electrolytes, and urinalysis every 4–6 months Blood pressure 3 times weekly	Avoid CS ACEi, ARB, CCB, ERA
Digestive	Esophageal dysmotility	64–90%	Dysphagia, odynophagia, heartburn, regurgitation, chronic cough (microaspiration), esophageal dilatation	Older age, dcSSc, ACA, Scl-70	Esophageal manometry, endoscopy (always if dysphagia), barium swallow	Proton pump inhibitor, H2 antagonist, prokinetic drugs, sucralfate
	GERD		Dyspepsia, Barrett's esophagus, strictures, reflux esophagitis			
	Intestinal and gastric dysmotility		Malabsorption, bloating, early satiety, SIBO, nausea, vomiting, pain, diarrhea/constipation, fecal incontinence (sphincter dysfunction), weight loss		Breath test, gastric emptying (GE) by scintigraphy, simple radiology or computerized tomography scan, ano-rectal manometry and/or endo-anal ultrasound	Prokinetic drugs, antibiotics courses (SIBO), nutrition supplementation (oral, enteral, or parenteral), ano-rectal biofeedback (incontinence)
	GAVE	5.7–22.3%	GI bleeding, iron deficiency anemia	ACA, anti-RNAP3	Gastroscopy ("watermelon stomach")	APC, RFA, and EBL

(continued)

Table 6.2 (continued)

Organ system affected	Complications	Prevalence	Clinical features	Risk factors	Screening and monitoring	Treatment
Urogenital	Male sexual dysfunction	>80%	Erectile dysfunction, penile deformities, and/or rigidity	Stress, older age, smoking, hypercholesterolemia, arterial hypertension	IIEF-5 questionnaire	PDE5-i
	Female sexual dysfunction	>50%	Discomfort, dyspareunia, and impaired sexual activity	Longer disease duration, depressive symptoms	FSFS questionnaire, FSDS	Lubricants

ACEi: angiotensin-converting enzyme inhibitor, AHSCT: autologous hematopoietic stem cell transplantation, APC: argon plasma coagulation, ARB: angiotensin receptor blocker, BNP: B-type natriuretic peptide, CCB: calcium channel blocker, CPM: cyclophosphamide, CS: corticosteroid, DLCO: diffusing capacity for carbon monoxide, EBL: endoscopic band ligation, ECG: electrocardiogram, ERA: endothelin receptor antagonists, FSFI: Female Sexual Function Index 300, FSFS: Female Sexual Function in SSc 306, FSDS: Female Sexual Distress Scale, FVC: forced vital capacity, GERD: gastroesophageal reflux disease, HCQ: hydroxychloroquine, HRCT: high-resolution computed tomography, GAVE: gastric antral vascular ectasia, IIEF-5: International Index of Erectile Function, ILD: interstitial lung disease, MMF: mycophenolate mofetil, MRI: magnetic resonance imaging, MTX: methotrexate, PAH: pulmonary arterial hypertension, PDE5-I: phosphodiesterase 5 inhibitors, PFT: pulmonary function tests, PDN: prednisolone, RFA: radiofrequency ablation, RNAP3: RNA polymerase III, RTX: rituximab, anti-Scl-70: anti-topoisomerase I antibody, SIBO: small intestinal bacterial overgrowth syndrome, SRC: scleroderma renal crisis, TCZ: tocilizumab, TFRs: tendon friction rubs, TnI: troponin

[a] The DETECT algorithm is a screening tool for pulmonary artery hypertension that uses pulmonary function tests (FVC and DLCO), serum urate, ECG, serum NTproBNP, and other features to provide a predictive score and guide further investigation. A right heart catheter may be indicated

Classification Criteria. SSc Phenotypes by Skin Subsets and Visceral Involvement

The evolution of SSc classification has followed a trajectory aimed at embracing broader patient categorization, characterized by distinct phases in its development. The original criteria, formulated in 1980 by the American College of Rheumatology (ACR) [1], were intentionally specific rather than sensitive, an approach chosen to reduce false-positive diagnoses. Consequently, these criteria focused on unequivocal SSc cases, thereby excluding early forms and lcSSc due to reduced sensitivity.

A subsequent milestone arrived in 1988 when LeRoy et al. proposed a SSc subclassification grounded in the scope of cutaneous involvement [13]. This classification scheme delineated two subsets: lcSSc and dcSSc, thereby setting the stage for a more nuanced understanding of the disease's manifestations.

The pursuit of classifying SSc confronted the challenge posed by patients who demonstrated a clear clinical profile of SSc yet did not meet the ACR's preliminary classification criteria. In 2001, LeRoy and Medsger recommended a classification scheme that categorized SSc patients into discrete subsets: lcSSc, dcSSc, and limited SSc (early SSc or prescleroderma) (preSSc) [14] (Table 6.3). The suggestion emerged that many within this group embodied "early SSc," a subset liable to develop into definite SSc during follow-up. A subsequent extensive prospective study on individuals presenting Raynaud's phenomenon affirmed that a substantial majority of early SSc patients indeed progressed to definite SSc, especially when both atypical nailfold capillaroscopy findings and SSc-specific autoantibodies were present [15], thereby validating the LeRoy and Medsger criteria for early SSc. They also highlighted another distinctive subset, characterized by the coexistence of Raynaud's phenomenon, scleroderma-associated autoantibodies, and internal organ involvement, yet lacking cutaneous sclerosis. This particular subgroup was termed "limited SSc without cutaneous involvement" and was introduced as "SSc sine scleroderma" (ssSSc) by Poormoghim et al. [16] (Table 6.3). The status of this subset underwent initial deliberation by LeRoy and Medsger, eventually leading to its incorporation within the spectrum of limited cutaneous SSc (lcSSc) due to analogous prognostic implications. Nevertheless, some investigators have identified discernible clinical distinctions between lcSSc and ssSSc [17].

In response to the imperative to predict which among these patients might eventually progress to SSc, the European Scleroderma Trial and Research (EUSTAR) group introduced in 2011 the concept of Very Early Diagnosis of Systemic Sclerosis (VEDOSS) based on "puffy swollen digits turning into sclerodactyly," in conjunction with Raynaud's phenomenon and positive antinuclear antibodies [18].

The collaboration between ACR and EULAR culminated in the formulation of the 2013 classification criteria [19] (Table 6.4). By combining elements from the 1980 and 2001 criteria and incorporating novel components, this iteration substantially enhanced sensitivity and specificity, findings

Table 6.3 SSc disease subsets extending the LeRoy and Medsger classification

Items	dcSSc	lcSSc	*Sine*	Early SSc	Prescleroderma
ACR/EULAR criteria 2013	≥9	≥9	≥9	Not always ≥9	<9
Skin fibrosis	Proximal	Distal to elbows and knees and/or face	–	–	–
RP	+	+	+	+	+
AAs	Scl-70, RNAP3, fibrillarin	ACA	+	+	+/–
NVC	Late pattern (Cutolo)	Active pattern (Cutolo)	Active pattern (Cutolo)	+	+/–
DU/pitting scars	+	++	+	+/–	–
Telangiectasia	–	++	+/–	+/–	–
Calcinosis	+	++	+/–	+/–	–
Arthritis	+	++	+/–	+/–	–
Esophageal dysmotility	++	+	+	GERD, HLES	–
PAH	+/–	++	+/–	No	–
ILD	++	+/–	+/–	No (but DLCO<80)	–
Cardiac	Fibrosis	+/– diastolic dysfunction	+/– diastolic dysfunction	+/– diastolic dysfunction	–
Kidney involvement/ SRC	+	+/–	+/–	–	–

AAs auto-antibodies, *DLCO* diffusing capacity for carbon monoxide, *DU* digital ulcers, *GERD* gastroesophageal reflux disease, *HLES* hypotonic lower esophageal sphincter, *ILD* interstitial lung disease, *NVC* nailfold videocapillaroscopy, *PAH* pulmonary arterial hypertension, *SRC* scleroderma renal crisis, *VEDOSS* very early diagnosis of systemic sclerosis

Table 6.4 The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)

Items	Sub-items	Weight/score[a]
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)	–	9
Skin thickening of the fingers (count the higher score)	Puffy fingers	2
	Sclerodactyly	4
Fingertip lesions (count the higher score)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease (maximum score is 2)	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
SSc-related autoantibodies	Anticentromere	3
	Anti-topoisomerase I	3
	Anti-RNA polymerase III	3

The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy)

[a] The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥9 are classified as having definite SSc

that have been corroborated in several cohorts. Nonetheless, some patients characterized by Raynaud's phenomenon and predictive factors did not fit the 2013 criteria, mirroring characteristics of the limited SSc group. Prudent application of these criteria, avoiding their misapplication to conditions like morphea, remains imperative. Although not explicitly designed to delineate subsets, heightened criteria sensitivity could conceivably aid in identifying subsets showcasing analogous clinical presentations and outcomes, thereby addressing SSc's inherent heterogeneity.

Association with Malignancy

The robust correlation between systemic sclerosis (SSc) and cancer underscores the importance of regular cancer surveillance for SSc patients, especially among older individuals and those with risk factors like RNAP-3 antibodies, unresponsiveness to treatment, constitutional symptoms, history of alkylating agent use, cytopenia, or familial cancer history. For patients with RNAP-3 antibodies, a specific algorithm suggests baseline clinical and instrumental tests, along with targeted lung, colon, breast, and prostate assessments. Positron emission tomography/computed tomography (PET/CT) is reserved for high-risk cases [20]. It's crucial to acknowledge the established two-phase relationship between SSc and cancer.

Considerations and Future Directions

Early Treatment Dilemma and Current Clinical Strategy

- The primary concern lies in overtreating patients who may not develop full-fledged SSc or whose progression might be slow. The central question revolves around the rationale for immunosuppression in patients with vasculopathy features only (e.g., Raynaud's phenomenon, modified nailfold capillaroscopy) or isolated clinical symptoms such as puffy fingers.
- The current approach for very early SSc is a rigorous monitoring program to promptly detect early internal organ involvement. Patients with mild clinical indications should be closely monitored, with a readiness to adjust therapeutic strategies upon progression to severe disease.

Need for Definitive Biomarkers for Predicting Disease Evolution

Variability in Disease Progression and Role of Internal Organ Involvement

- Aggressive SSc cases, like dcSSc, enable decisive treatment against disease progression and mortality risk, while lcSSc's slower course can mask organ involvement, eluding early detection.
- The interval between Raynaud's onset and non-Raynaud symptoms offers a diagnostic "window of opportunity" for very early SSc diagnosis.

Considerations for Classification Criteria

- Age of onset, genetics, race, and geography should influence classification criteria.
- Inclusion of multiple antibodies (AAs) must account for serological diversity.
- Genomics, proteomics, and metabolomics, as well as integrative bioinformatics, can improve classification criteria and provide the groundwork for personalized medicine.

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Sjögren Disease

7

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Abstract

In 1933, the Swedish ophthalmologist Hendrik Sjögren was the first to suggest that behind the dryness that several of his patients presented, there could be a systemic disease related to an abnormal immune response. Since then, the term Sjögren's disease (SjS) has been used and it has been considered a minor and infrequent disorder compared to other systemic autoimmune diseases (SAD) and, consequently, with little progress both in clinical and therapeutic research. However, despite SjS causing dysfunction of the exocrine secretory glands with consequent dryness of the main mucosal surfaces this disease can also affect internal organs and increase the risk of developing hematological malignancies. Criteria have been proposed for the correct classification of patients and are based on the main diagnostic tools for SjS diagnosis. Herein, after a brief description of SjS pathophysiology, these criteria are extensively discussed.

Keywords

Sjögren disease · Autoimmune epithelitis · Classification criteria · Autoantibodies · Salivary gland biopsy

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Description

Sjögren disease (SjS) is a systemic autoimmune disease with a specific predisposition for causing inflammation of the exocrine glands, predominantly the salivary and lacrimal glands but also including the nose, upper respiratory tract, oropharynx, and, in women, the vagina. The main consequence of this inflammation is the development of sicca symptoms, such as dryness of the mucosal surfaces, principally in the mouth and eyes [1]. The disease is diagnosed overwhelmingly in middle-aged women (95%), with a recent Big Data study reporting a female/male ratio of 10:1 [2]. The phenotypic expression at the time of diagnosis is strongly linked to age, with a higher frequency of glandular-adenopathic involvement and immunological markers the younger age at diagnosis, and of dry mouth and pulmonary involvement the older age [3]. Ethnic and geographic factors also play a role, including younger age at diagnosis and greater systemic activity in black/African-American people, greater involvement in women and less frequency of sicca in Asian people, or greater systemic activity in people from countries of the south of each continent [4, 5].

The disease is caused by imbalance in the immune system, although the main etiopathogenic factors have not been identified. Viruses have been considered for decades as factors that could initiate the autoimmune etiopathogenic process, especially those that can latently infect the salivary glands [6]. Drugs such as checkpoint inhibitors used in cancer patients have also been implicated and produce a disease similar to SjS, although with a very different profile (mostly men and with a predominantly immunonegative serological profile) [7]. SjS is considered a non-hereditary polygenic disease and, therefore, it is rare to see cases diagnosed in the same family, although the risk of developing the disease is between 10 and 20 times higher in siblings, parents, and children of people with SjS. The most widely accepted etiopathogenic model currently focuses on the development of autoimmune epithelitis [8, 9], which would be initiated by the hyperactivity of the type I inter-

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feron system triggered by external noxa (viruses, toxins) [1]. The consequence would be an abnormal response of T and B lymphocytes to autoantigens abnormally expressed by the glandular epithelium (e.g., Ro and La ribonucleoproteins), with the subsequent release of proinflammatory cytokines and other mediators [10].

The phenotypic expression of the disease is broad, although the main clinical presentations are the predominant involvement of dryness (the most common), the predominance of general involvement characterized by chronic fatigue and tiredness, or multiorgan autoimmune involvement, which includes systemic manifestations that may be the first manifestation of the disease (Table 7.1 [3]) [3].

Table 7.1 Baseline characteristics of 12,753 patients with primary Sjögren's disease. Analysis of patients from the Sjögren Big Data Consortium

Variable	Patients with SjS (*n* = 12,753)
Age at diagnosis (*n* = 12,719) (mean ± SD)	52.2 ± 14.6
Sex (female)	11,918 (93.5)
Ethnicity (*n* = 12,747)	
White	9169 (71.9)
Asian	2059 (16.2)
Hispanic	734 (5.8)
Black/African-American (AA)	178 (1.4)
Others	607 (4.8)
Geolocation	
Europe	8844 (69.3)
America	1760 (13.8)
Asia	1880 (14.7)
Other	269 (2.1)
Signs and symptoms at presentation	
Dry eye	11,723 (91.9)
Dry mouth	11,891 (93.2)
Diagnostic tests	
Abnormal ocular tests (any) (*n* = 10,834)	9070 (83.7)
Schirmer's test (*n* = 10,720)	8391 (78.3)
Rose bengal score/other ocular dye score (*n* = 5103)	3643 (71.4)
Abnormal oral diagnostic tests (any) (*n* = 9665)	7637 (79.0)
Unstimulated whole salivary flow (*n* = 7758)	5908 (76.2)
Parotid sialography (*n* = 2416)	1954 (80.9)
Salivary scintigraphy (*n* = 2282)	1846 (80.9)
Positive minor salivary gland biopsy (*n* = 9045)	7431 (82.2)
Immunological profile	
ANA-positive (*n* = 12,020)	9713 (80.8)
RF-positive (*n* = 10,424)	5047 (48.4)
Positive anti-Ro/La antibodies (*n* = 12,630)	9714 (76.9)
Anti-Ro antibodies (*n* = 12,624)	9431 (74.7)
Anti-La antibodies (*n* = 12,564)	5641 (44.9)
Low C3 levels (*n* = 10,392)	1332 (12.8)
Low C4 levels (*n* = 10,376)	1380 (13.3)
Positive cryoglobulins (*n* = 5614)	428 (7.6)
Systemic activity	
Mean ESSDAI score (*n* = 11,724)	5.9 ± 7.3
DAS (*n* = 11,724)	
No activity (ESSDAI = 0)	2239 (19.1)
Low	4471 (38.1)
Moderate	3604 (30.7)
High	1410 (12.0)
ESSDAI domains (score >=1) (*n* = 12,152)	
Constitutional	1200 (9.9)
Lymphadenopathy	1055 (8.7)
Glandular	2487 (20.5)
Articular	4493 (37.0)
Cutaneous	1115 (9.2)
Pulmonary	1258 (10.4)
Renal	513 (4.2)
Muscular	262 (2.2)
PNS	693 (5.7)
CNS	220 (1.8)
Hematological	2619/11,986 (21.9)
Biological	5817/11,800 (49.3)

Retamozo S, Acar-Denizli N, Horváth IF, Ng WF, Rasmussen A, Dong X, et al. Influence of the age at diagnosis in the disease expression of primary Sjögren syndrome. Analysis of 12,753 patients from the Sjögren Big Data Consortium. Clin Exp Rheumatol. 2021;39 Suppl 1:166–74 [3]

Glandular Involvement

Enlargement of the parotid glands, which is not one of the typical sicca symptoms, is the predominant feature observed at presentation in children with SjS [1]. Dry eyes and mouth are the most common symptoms of the disease (90%). The lack of saliva produces a dry mouth and impairs the ability to speak and swallow food, increasing the risk of developing cavities [11]. Typically, one-quarter of patients experience dry eye syndrome, which initially prompts the patient to seek medical attention. Glandular dysfunction also causes dryness of the upper respiratory tract and oropharynx, of the skin, and vaginal dryness. Acute inflammation of the glands is typically observed in the parotid glands (10–20%), and it is highly indicative of the disease if it is accompanied by sicca syndrome (Figs. 7.1 and 7.2) [3, 12].

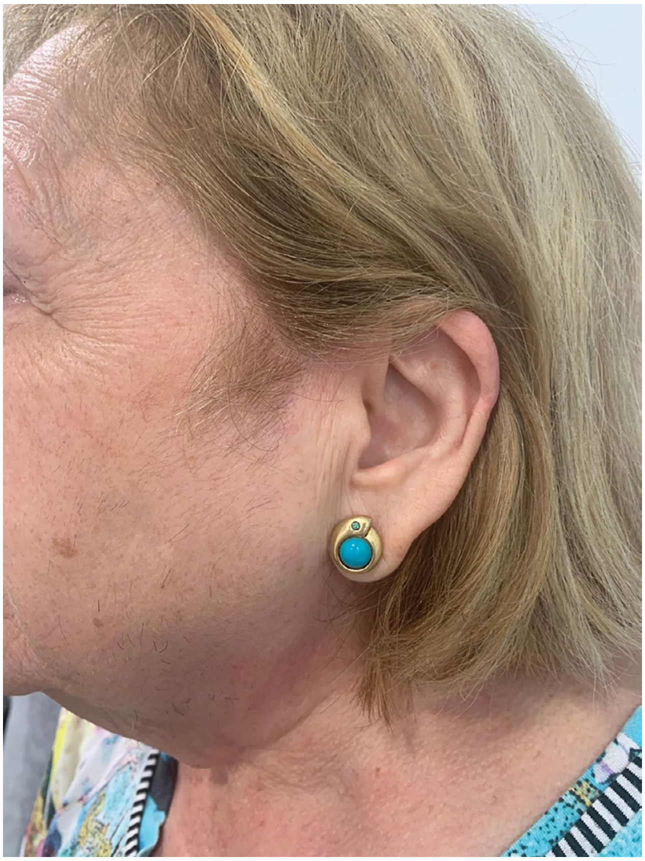

Fig. 7.1 Parotid enlargement in a patient with Sjögren's disease. (Own photograph taken with the patient's consent)

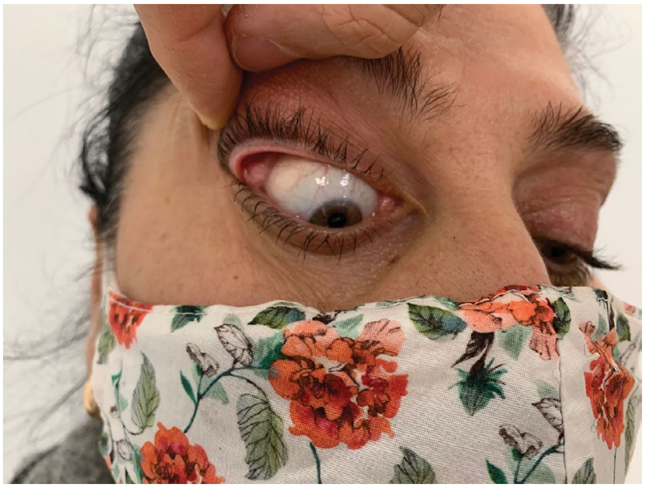

Fig. 7.2 Lacrimal gland enlargement in a patient with Sjögren's disease. (Own photograph taken with the patient's consent)

General Symptoms and Organ-Specific Complications

Typical symptoms are chronic fatigue and musculoskeletal pain, which can have a much greater impact on quality of life for some people than symptoms of dryness. It is a very nonspecific syndromic profile common to other diseases especially chronic fatigue syndrome, fibromyalgia, which also predominantly affect the same epidemiological portion of the population. No study has confirmed a strong etiopathogenic autoimmune link with SjS beyond this epidemiological overlap (30%), in which SjS usually has a seronegative immunological profile and less systemic involvement [11].

SjS can also be associated with systemic symptoms (Table 7.2, [1]), which can be seen in approximately 50–60%

Table 7.2 Organ-by-organ systemic manifestations

Oral symptoms
• Hyposalivation
• Soreness
• Adherence of food to the mucosa
• Dysphagia
• Difficulties in speaking or eating
• Dental caries
• Oral candidiasis
Ocular symptoms
• Insufficient tears
• Inability to tear
• Foreign-body sensation
• Conjunctival inflammation (keratoconjunctivitis sicca)
• Eye fatigue
• Decreased visual acuity
• Blepharitis
• Bacterial keratitis
General symptoms
• Fatigue
• Chronic pain
• Low-grade fever
• Weight loss
Lymph node complications
• Reactive multiple lymphadenopathy (swelling of the lymph nodes)
• Lymphoproliferative complications
Cutaneous complications
• Cutaneous vasculitis (10% of patients)
• Purpura
• Cutaneous ulcers[a]
• Annular erythema (9% of patients)
• Xerosis cutis (abnormally dry skin; 23–68% of patients)
Articular and muscle complications
• Arthralgias (joint pain; 60–70% of patients)
• Non-erosive symmetric arthritis
• Subclinical synovitis (20–30% of patients)
• Jaccoud arthropathy (non-erosive joint disorder)[b]
• Myalgias (20–40% of patients)

(continued)

of patients. Severe clinical manifestations have been described in 15–20% of patients with SjS, whereas the prevalence of lymphoma has been estimated at around 5%. According to the European League Against Rheumatism (EULAR) SjS Disease Activity Index (ESSDAI; disease score ranging from 0 to 123), systemic features of SjS can be described by recognizing various organ domains at different levels of disease activity [2, 11].

Table 7.2 (continued)

• Myositis[b]
Pulmonary complications
• Chronic obstructive lung disease
• Bronchiectasis
• Interstitial lung diseases[a]
• Pleuritis[b]
Cardiovascular complications
• Raynaud phenomenon (13% of patients)
• Pericarditis[b]
• Pulmonary arterial hypertension[a,b]
• Dysautonomia
• Cryoglobulinemic vasculitis[a]
Pancreatic complications
• Recurrent acute pancreatitis
Nephro-urological complications
• Renal tubular acidosis (9% of patients)
• Glomerulonephritis (4% of patients)[a]
• Interstitial cystitis (in the absence of bacterial infection)
• Osteomalacia
• Recurrent renal colic due to renal stones
• Hypokalemic paralysis[a]
Peripheral nervous system complications
• Mixed polyneuropathy
• Axon sensory polyneuropathy
• Sensory ataxic neuronopathy[a]
• Axon sensorimotor polyneuropathy
• Trigeminal or other cranial neuropathies
• Demyelinating polyradiculoneuropathy
• Autonomic neuropathy
• Pure sensory neuronopathy
• Mononeuritis multiplex[a]
• Small-fiber neuropathy (painful paresthesias)
Central nervous system complications
• White matter lesions (multiple sclerosis-like disease)[a]
• Neuromyelitis optica spectrum disorder[a]
• Recurrent aseptic meningitis
Hematological complications
• Hemolytic anemia[a,b]
• Unexplained leukopenia (lymphopenia and neutropenia)
• Unexplained thrombocytopenia[a]
• Evans syndrome[b]
• Unexplained monoclonal gammopathy
• Thrombotic thrombocytopenic purpura[a,b]
• B-cell lymphoma[a]
Obstetrics
• Autoimmune congenital heart block[a]
• Cardiac fibroelastosis
• Unexplained fetal valvular disease
• Neonatal lupus
Ear, nose, and throat complications
• Recurrent parotid enlargement
• Bilateral multicystic parotid masses
• Sensorineural hearing loss
• Parotid lymphoma[a]

Brito-Zerón P, Baldini C, Bootsma H, Bowman SJ, Jonsson R, Mariette X et al. Sjögren syndrome. Nat Rev Dis Primers. 2016; 2:16047 [1]

[a] Denotes severe systemic manifestations

[b] Denotes rarely reported manifestations (<1% of patients) or suggesting polyautoimmunity (i.e., the coexistence of other systemic autoimmune diseases)

Diagnosis

Glandular Dysfunction

The symptoms of dryness are related to the hypofunction of the main affected glands (salivary and lacrimal), which must be observed with specific diagnostic examinations [11] (Table 7.3 [11]). The function of the major salivary glands is evaluated indirectly by measuring salivary flow (amount of saliva produced in a predefined time, with or without prior glandular stimulation), or directly by means of salivary gland scintigraphy (determines the pattern of uptake and secretion by said glands of a radioactive marker, technetium 99m) [11]. The use of ultrasound as a diagnostic tool has been implemented in recent years, and finding glandular ultrasound patterns of heterogeneous appearance that show glandular infiltration is useful, although standardized and internationally accepted diagnostic criteria are still far from being achieved [13]. PET-CT is especially useful for the study of lymphoproliferative processes, although it can also show uptake of the parotid glands. Lacrimal gland function is assessed using the Schirmer test (amount of lacrimal secretion in 5 min), and analysis of the corneal surface using dyes (fluorescein and lissamine green corneal stains), which reveal the damage produced on the corneal surface. The evaluation of the function of the glands is essential before starting the treatment of dryness [14].

Laboratory Studies

One out of three patients present with cytopenia (mainly mild neutropenia and lymphopenia), and 20–40% with elevated erythrocyte sedimentation rate (often with normal C-reactive protein values) and hypergammaglobulinemia. The detection of these three analytical abnormalities is highly indicative of SjS [11].

Immunological Profile

Autoantibodies are the key serological markers of most autoimmune diseases and in patients with SjS they can be

Table 7.3 Main diagnostic tests to investigate the salivary and lacrimal glands in Sjögren's disease

Diagnostic tests	Technical team	Abnormal values	Practical issues
Unstimulated salivary flow rate	Graduated test tube	Production less than 1.5 mL for 15 min (<0.1 mL/min)	Results may be influenced by age, disease duration, comorbidities, temperature, or medications
Stimulated salivary flow rate	Graduated test tube	Production less than 0.2–0.3 mL/min for 15 min	Better correlation with histopathological alterations of structural glandular lesion
	Chewing gum or lemon juice		
Salivary scintigraphy	Radioactive tracer, technetium 99m	Schall's categorical classification in 4 grades (from normal to severe)	Severe affectation (grade IV) at the time of diagnosis is associated with greater systemic activity and worse evolution
	Scintigraphic camera		
Parotid ultrasound	Sonographer Broadband linear transducers (average frequency above 10 MHz)	Structural changes (hyperechogenic and hypoechogenic areas, inhomogeneity, and altered echogenicity in general)	Progressive increase in data in favor of its use in initial diagnostic phases; important role in ruling out abscesses and tumors
Schirmer test I	Filter paper (No. 41 Whatman)	Paper moisture <5 mm 5 min	Evaluate basal secretion
	Anesthesia		
Schirmer test II	Filter paper (No. 41 Whatman)	Paper moisture <10 mm 5 min	Measures baseline plus reflex secretion
Corneal staining	Stains (fluorescein and lissamine green)	Van Bijsterveld score ≥4	Rose Bengal has been replaced by lissamine green (much better tolerated dye)
	Slit lamp	Oxford scale score ≥III	
	Cobalt blue filter	Ocular Staining Score (OSS) ≥3	Some studies show an increase in the abnormal OSS score to 5

Brito-Zerón P, Retamozo S, Ramos-Casals M. Sjögren syndrome. Med Clin (Barc). 2023; 160:163–171 [11]

detected up to 20 years before the diagnosis of the disease [1]. Although antinuclear antibodies (ANA) are the most frequently detected autoantibodies in primary SjS (>80%), their specificity is very low due to the high frequency in patients with non-specific symptoms and even in healthy people [11]. Rheumatoid factor (RF) is present in half of the patients and has greater specificity than ANA, since it can predict the development of SjS and is related to systemic activity [15].

Anti-Ro and anti-La antibodies are the immunological markers of the disease. Anti-Ro are the most frequent (50–80% depending on the technique used) and recognize 2 proteins associated with small RNA molecules (Ro60 and Ro52). Since the standard immunological test (Ro/SS-A) mainly detects antibodies against Ro60, in 10–20% of SjS patients with a negative Ro/SS-A determination, specific antibodies against Ro52 can be identified [11]. Anti-Ro antibodies are strongly associated with the risk of developing SjS, are associated with an earlier onset and a more severe systemic course, and are especially useful in those people (especially young people) in whom the disease begins with systemic involvement [11]. Anti-La antibodies can be detected along with anti-Ro antibodies in more than 95% of cases. Although the presence of these antibodies in isolation has been eliminated as a classification criterion for the disease, in daily practice the clinical diagnosis of SjS must be made in these patients [16].

Cryoglobulins are immunoglobulins that precipitate in vitro at temperatures <37 °C and are detected in 10% of patients with primary SjS [11]. They are mostly mixed cryoglobulins and the immunological marker associated with a worse prognosis of the disease, including a greater risk of developing systemic disease and lymphoma, and lower survival [17]. Indirect laboratory data reveal underlying mixed cryoglobulinemia including low C4 levels, elevated RF, and serum IgMk monoclonal gammopathy. Hypocomplementemia (low levels of C3 and/or C4) is detected in 10–15% of patients and is also associated with a worse outcome, as are circulating monoclonal immunoglobulins (5–10%) [11].

Salivary Gland Biopsy

The histological hallmark of SjS is focal lymphocytic infiltration of the salivary glands, which is defined as the presence of at least one dense aggregate of ≥50 lymphocytes in perivascular or periductal areas, and which are made up of T lymphocytes, with less presence from other cells (B lymphocytes, natural killer, and dendritic cells). In advanced cases, acinar epithelial cell atrophy and fibrosis can be observed. The technique for biopsy of minor salivary glands with the best balance between efficacy and safety is linear incision (not puncture) on the buccal side of the lower lip [11].

Classification Criteria

The current classification criteria are the American-European (AE) published in 2016, which include the presence of anti-Ro antibodies or a positive salivary biopsy as mandatory criteria (Table 7.4 [11, 18]) and which, for the first time, allow the classification of patients without symptoms of dryness that presents with systemic involvement, with a sensitivity of 96% and a specificity of 95%, figures somewhat higher than those of previous criteria [18].

Criticism on the Diagnostics Criteria

Autoantibodies are the only laboratory criterion included in the three last international classification criteria for SjS proposed since 1993, although the number has been reduced progressively. The 1993 European included four antibodies (ANA, RF, Ro/SSA, and/or La/SSB), the 2002 Criteria 2 (anti-Ro/SSA and anti-La/SSB), and the 2016 ACR/EULAR, only one (Ro/SSA). Despite the progressive restrictive inclusion of autoantibodies, sensitivity/specificity figures obtained by each set of criteria were quite similar. After the exclusion of the La/SSB autoantibodies from the 2016 criteria, sensitivity and specificity were 96%/95%, respectively, while for the 2002 criteria, the figures were 96%/94%.

Anti-La/SSB antibodies are detected in 45% of patients, and their concomitant presence with anti-Ro/SSA antibodies has been associated with a higher frequency of abnormal diagnostic tests and higher mean ESSDAI scores in comparison with immune-negative patients. Anti-La/SSB antibodies have a high diagnostic specificity for SjS and Theander et al.

Table 7.4 2016 ACR/EULAR criteria for the classification of Sjögren's syndrome

PREVIOUS REQUIREMENTS	
1. Absence of associated systemic diseases	
Previous diagnosis of any of the following situations, which would exclude the diagnosis of SS in clinical trials or therapeutic trials, due to overlapping clinical features or interference with diagnostic criteria:	
• History of radiation therapy to the head and neck	
• Active HCV infection (PCR confirmation)	
• HIV infection	
• Sarcoidosis	
• Amyloidosis	
• Graft-versus-host disease	
• IgG4-related disease	
2. Symptoms of dry eyes and/or mouth	
At least one positive response to one of the following questions:	
• Have you had daily dry eye and persistent discomfort for more than 3 months?	
• Do you have a recurring feeling of grit in your eyes?	
• Do you use tear substitutes more than 3 times a day?	
• Have you had a daily feeling of dry mouth for more than 3 months?	
• Do you drink fluids frequently to help swallow dry foods?	
3. Systemic disease	
In the absence of symptoms of dryness, presence of systemic disease (at least one domain with a positive item in the ESSDAI classification)	
RANKING SCORE	
To be classified as primary SS, the patient must present a score ≥4 when the individual scores of the 5 criteria described below are added together [1]	
Criteria	**Score**
Labial salivary gland with focal lymphocytic sialadenitis and ≥1 focus in 4 mm^2[a]	3
Anti-SSA/Ro positive	3
Ocular staining score ≥5 (or van Bijsterveld score ≥ 4) in at least 1 eye[b,c]	1
Schirmer test ≤5 mm/5 min in at least 1 eye[b]	1
Total unstimulated salivary secretion ≤0.1 mL/min[d]	1

Brito-Zerón P, Retamozo S, Ramos-Casals M. Sjögren syndrome. Med Clin (Barc). 2023; 160:163–171 [11]

Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome. Ann Rheum Dis. 2017; 76:9–16 [18]

[a] Histopathologic examination should be performed by a pathologist with experience in the diagnosis of focal lymphocytic sialadenitis and scoring using the Daniels protocol

[b] Patients regularly taking anticholinergic medications should be evaluated for objective signs of salivary hypofunction and dry eyes after a sufficient interval without these medications to consider a valid measure of oral and ocular dryness

[c] Ocular staining score described by Whitcher et al.; Van Bijsterveld score described by van Bijsterveld

[d] Measurement of unstimulated total salivary flow described by Navazesh and Kumar

reported that the predictive value for developing the disease was highest in asymptomatic carriers of anti-La/SSB antibodies (OR = 34) than in those carrying anti-Ro60 antibodies (OR = 30). The etiopathogenic central role of the La/SSB autoantigen in SjS, confirmed by several studies published in the last 20 years, clearly supports the inclusion of La/SSB autoantibodies into the typical immunological spectrum of the disease [16]. A recent interest in characterizing SjS patients carrying isolated La/SSB autoantibodies has emerged after the exclusion of this subset of patients from the recently proposed AE classification criteria [18]. This exclusion was based on the manuscript published by Baer et al. in the SICCA cohort reporting that patients with isolated La/SSB antibodies had lower ocular staining and salivary focus scores in comparison with the seronegative group, although they also had a higher frequency of dry mouth, higher median Schirmer test and a higher frequency of abnormal unstimulated whole saliva flow results. Comparisons were made among patients with a suspected SjS (either primary or associated), and among the 3514 SICCA participants enrolled, only 45% fulfilled the 2002/2012 criteria. In contrast, another study carried out in SjS patients compared the clinical manifestations of 29 anti-Ro/SSA-negative, anti-La/SSB-positive subjects to the manifestations found in other immunological subgroups and found no significant differences for the objective findings of lacrimal or salivary gland dysfunctions, although those carrying isolated La/SSB autoantibodies had a lower mean age at diagnosis and some systemic features were numerically less frequent, especially joint disease and persistent cough, in comparison with those carrying Ro/SSA autoantibodies [16]. In the largest reported cohort of patients (Big Data Sjogren Consortium) with SjS fulfilling the 2002 AE classification criteria, only 3% carried isolated anti-La/SS-B antibodies. These patients had a systemic SjS phenotype that mixed some features characteristic of both immunonegative patients and patients carrying isolated anti-Ro/SS-A antibodies [19].

Pre-existing lymphoma has been traditionally considered an exclusion criterion for classification as SjS, an erroneous concept that has recently been corrected by the 2016 ACR/EULAR classification criteria. A recent study has examined whether there are differences in lymphoma characteristics depending on whether it was diagnosed before or after confirming SjS. Patients first diagnosed with lymphoma were more frequently male, and had a higher frequency of enlarged lymph nodes, MALT lymphoma, and salivary gland lymphoma [19].

Treatment

Glandular Involvement

For oral dryness, non-pharmacological stimulation using taste stimulants and/or mechanical stimulants is recommended in people with mild glandular dysfunction. In patients with moderate dysfunction, pharmacological stimulation with muscarinic agonists can be considered, an indication to be carefully considered due to the unfavorable safety profile of these drugs. It is not recommended for patients without residual glandular function (severe glandular dysfunction), in whom only saliva substitutes would be considered. Regarding dry eyes, the first option is volume replacement and lubrication using artificial tears and eye gels. Patients with severe or refractory dry eyes should always be treated by an ophthalmologist, who may initially consider short courses of ocular topicals containing NSAIDs or corticosteroids. The use of immunosuppressive eye drops such as cyclosporine A is considered in patients with refractory severe dry eye. The efficacy of autologous serum is more controversial and is usually used as a last option. For the treatment of dryness, the use of systemic therapies is not recommended [14].

Systemic Involvement

In people with frequent episodes of acute musculoskeletal pain, the use of hydroxychloroquine has been proposed. In patients with daily non-inflammatory chronic pain, the chronic use of analgesics and anti-inflammatories should be avoided, and it is recommended to follow the same recommendations as those proposed for idiopathic chronic pain recommendations to apply also for chronic fatigue [14]. The use of systemic therapies should be restricted to the person with active systemic disease. It usually consists of a sequential regimen that includes a first phase of intensive immunosuppressive therapy aimed at restoring organ function as soon as possible (remission induction), followed by a second course aimed at maintaining the initial therapeutic response (remission maintenance). As a general rule, for most systemic compromises, glucocorticoids (GC) can be considered the first-line option in patients with active systemic disease, and immunosuppressive and biologic agents as second/third-line options for use in GC-refractory or intolerant patients, those with severe disease or those in whom the use of GC is anticipated in the long term [14]. The lack of direct comparative studies of the main immunosuppressants used in SjS does not allow recommending the use of one agent over another, except when patient characteristics or comorbidities are considered with respect to the security profile. The biologic therapies in this century have increased the therapeutic arsenal available to treat severe SjS. The use of rituximab as a second or third line can be considered in patients with severe refractory systemic disease, especially those with cryoglobulinemic vasculitis, with the possible use of belimumab as a rescue option [14].

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8 Mixed Connective Tissue Disease

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Abstract

Mixed connective tissue disease (MCTD) is a systemic autoimmune disease characterized by clinical manifestations of systemic lupus erythematosus, systemic sclerosis, poly-/dermatomyositis, and rheumatoid arthritis. This chapter describes and analyses the available criteria for MCTD classification.

Keywords

Mixed connective tissue disease · MCTD · Diagnosis · Classification · Criteria · Anti-U1-RNP antibodies

Introduction

Mixed connective tissue disease (MCTD) is a systemic autoimmune disease described for the first time by Sharp et al. in 1972 as an entity characterized by a mixture of clinical features of systemic lupus erythematous (SLE), systemic sclerosis (SSc), rheumatoid arthritis (RA), and poly-/dermatomyositis (PM/DM) [1]. A recent epidemiological study on MCTD showed a female-to-male ratio of 3.3, mean age at diagnosis of 38 years, and incidence and prevalence of 0.2 and 3.8 per 100,000 individuals, respectively [2]. The presence of anti-U1-ribonucleoprotein (anti-U1-RNP) autoantibodies is regarded as the serologic hallmark of MCTD; however, such autoantibodies, even in high titre, are not pathognomonic for MCTD since they can be found also in patients with SLE (20–40%), SSc (2–14%), PM/DM (6–9%), and undifferentiated connective tissue disease (UCTD), thus lacking specificity [3]. Whether MCTD is a distinct entity or rather an overlap of two or more autoimmune disorders has remained a matter of debate for over 50 years; some support the former hypothesis due to the strong genetic association with HLA-DR4 observed in MCTD but not in other CTDs [4]. MCTD is characterized by wide heterogeneity in terms of clinical manifestations, and notably, up to 42% of patients may "evolve" into other CTDs over time through the so-called "clinical shift" [5]. The main clinical features, laboratory findings and serological markers of MCTD are summarized in Tables 8.1, 8.2 and 8.3, respectively. The apparent rarity of MCTD, the ongoing debate about its nature, the wide spectrum of signs and symptoms, and the possible phenotype instability during follow-up represent a challenge for diagnosis. Moreover, five different sets of criteria have been developed for MCTD, without one being internationally accepted as the "gold standard." Hence, currently, there is no universal consensus on how and when to diagnose and/or classify a patient with MCTD [5]. In this chapter, we describe and analyze the available criteria for MCTD.

Leucopenia and polyclonal hypergammaglobulinemia are frequently reported [5], although no large series provided their frequency.

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Table 8.1 Main clinical signs and symptoms in MCTD

Signs and symptoms	Frequency (%)
Mucocutaneous system	
Malar rash	24.3 [6] to 41 [2]
Raynaud's phenomenon	66.7 [6] to 99 [2]
Digital gangrene	4.5 [6]
Puffy hands	55.7 [7] to 93 [2]
Sclerodactyly	34 [2] to 43 [3]
Alopecia	27 [6]
Mucosal ulcers	30.6 [6]
Sicca syndrome	14.4 [6]
Musculoskeletal system	
Arthritis	69.4 [6] to 89.6 [7]
Myositis	32.5 [7] to 37.8 [6]
Pulmonary system	
Interstitial lung disease	35 [2] to 47.1 [7]
Pulmonary arterial hypertension	4 [2] to 17.8 [7]
Pleuritis	6.3 [6] to 14 [2]
Cardiovascular system	
Pericarditis	8.1 [6] to 12 [2]
Myocarditis	1.8 [6]
Gastrointestinal system	
Esophageal dysmotility	28.8 [6] to 50 [2]
Hematological system	
Lymphadenopathy	9.9 [6] to 13.7 [3]
Hemolytic anemia	18.9 [6] to 27 [2]
Thrombocytopenia	4.5 [6] to 12 [2]
Genitourinary system	
Glomerulonephritis	3 [2] to 17.1 [6]
Proteinuria	0.1 [8]
Neurological abnormalities	11.2 [3] to 20 [7]
Neuropathy	9 [6]
Seizure	3.6 [6]
Headache	8.1 [6]
Meningitis	2.7 [6]
Other	
Fatigue	24.3 [6]
Fever at presentation	45.9 [6]
Antiphospholipid syndrome	25.7 [7]

Table 8.2 Main laboratory findings in MCTD

Laboratory finding	Frequency (%)
Thrombocytopenia	4.5 [6] to 12 [2]
Hemolytic anemia	18.9 [6] to 27 [2]
Elevated CPK	19.2 [3] to 33 [2]
Hypocomplementemia	42 [8]
Raised inflammatory markers at presentation	13 [8]
Direct Coombs test	56.7 [6]

Table 8.3 Main serological findings in MCTD

Serological finding	Frequency (%)
Anti-U1-RNP antibody	100 [2, 6]
Antinuclear antibody (ANA)	89.2 [6] to 93.8 [3]
Anti-double-stranded DNA (Anti-dsDNA)	3.2 [7] to 27 [6]
Anti-Smith antibody (anti-Sm)	3.6 [6] to 17.2 [3]
Anti-SSA/Ro	10.8 [6] to 33.5 [7]
Anti-SSB/La	4.5 [6]
Rheumatoid factor (RF)	22.5 [6]
Anti-CCP (ACPA)	16.7 [3] to 18.9 [7]
Anti-Scl-70	1.8 [6] to 16.4 [3]
Anti-centromere antibody (ACA)	4.4 [3]
Lupus anticoagulant (LAC)	11.7 [6]
Anticardiolipin antibody	5.4 [6] to 35 [7]
Anti-β2-GPI antibody	28.2 [7]

Classification Criteria

The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have not yet provided classification criteria for MCTD. To date, five sets of criteria have been proposed for MCTD [9–13] which have been often referred to as "diagnostic criteria" [6, 14]. However, the term "diagnostic criteria" would imply the ideal situation of sensitivity and specificity of 100% and the consequent foolproof ability to rule in—or out—a disease. Since no set of available criteria for any rheumatic disorder, including MTCD, has ever shown perfect performance in this regard leading to a certain proportion of patients being always misclassified, the rheumatologist is the only one who can establish a diagnosis after examining the features of each patient. Considering such limitations, the ACR Diagnostic and Therapeutic Criteria Committee stressed the importance of employing the term "classification criteria" rather than "diagnostic criteria" when referring to CTDs [15]. Thus, the MCTD criteria herein described are referred to as "classification criteria" and are given in Table 8.4.

Although all sets of classification criteria for MCTD insist on the presence of high titers of anti-U1-RNP antibodies, they are distinctly different in many aspects [16]:

- Sharp's criteria [9] include several clinical manifestations of SLE, SSc, PM/DM, and RA. Importantly, they are the only set of criteria which emphasize that anti-Sm antibodies must be excluded to classify a patient as having MCTD.

- Alarcón-Segovia's criteria [10] are less numerous and include a set of five "core" clinical manifestations of MCTD.
- Kahn's criteria [11] are very close to Alarcón-Segovia's, except for the absence of acrosclerosis.
- Kasukawa's criteria [12] are an in-between of the previous ones as they require at least one out of 2 "core" manifestations plus at least one sign of ≥2 defined CTDs of the spectrum (SLE, SSc, PM/DM).

It remains controversial which set of criteria is the most sensitive and/or specific, as the reported accuracy of the different criteria varies across cohorts. The studies with the larger series of MCTD patients did not always employ all available sets of criteria [7], thus making it hard to have complete and comparable data. An old study claimed that Sharp's criteria were the most reliable because patients strictly fulfilling such criteria would extremely rarely evolve into defined CTDs during a follow-up period of 2–8 years [17]. However, it has been recently claimed that Kasukawa's criteria are the most sensitive and thus should be used to screen patients and rule out MCTD, while both Alarcón-Segovia's and Kahn's are the most specific and should be used to rule in MCTD [6]. A summary of all previously reported sensitivities and specificities for each set of criteria is provided in Table 8.5.

Table 8.4 MCTD classification criteria

Sharp [9]	*Major criteria* (1) Myositis (2) Raynaud's phenomenon and/or esophageal hypomotility (3) Swollen hands and/or sclerodactyly (4) Anti-ENA ≥1:10,000, positive for anti-U1-RNP antibodies AND negative for anti-Sm antibodies (5) DLCO <70% and/or PAH and/or proliferative vascular lesions on lung biopsy	*Minor criteria* (1) Alopecia (2) Leucopenia (3) Anemia (4) Pleuritis (5) Pericarditis (6) Arthritis (7) Trigeminal neuropathy (8) Malar rash (9) Thrombocytopenia (10) Mild myositis (11) History of swollen hands	*Requirements* **Certain MCTD**: 4 major criteria + no anti-Sm antibodies + anti-U1 RNP titer >1:4000 Probable **MCTD**: 3 major criteria and no anti-Sm antibodies, OR 2 major criteria plus 1 minor criterion plus anti-U1-RNP antibodies >1:1000
Alarcón-Segovia [10]	*Serological criterion* Anti-U1-RNP titer >1:1600 at the hemagglutinin assay	*Clinical criteria* (1) Swollen hands (2) Raynaud's phenomenon (3) Acrosclerosis (4) Synovitis (5) Myositis	*Requirements* Serological criterion present + ≥3 clinical criteria (either synovitis or myositis must be present)
Kahn [11]	*Serological criterion* High anti-U1-RNP titer, corresponding to speckled ANA titer of ≥1:2000 at the hemagglutinin assay	*Clinical criteria* (1) Swollen hands (2) Raynaud's phenomenon (3) Synovitis (4) Myositis	*Requirements* Serological criterion present + Raynaud's phenomenon + ≥2 of swollen hands, synovitis, and myositis
Kasukawa [12]	*Serological criterion* Anti-U1-RNP positivity *Common symptoms* (1) Raynaud's phenomenon (2) Swollen fingers	*Mixed signs/symptoms* **SLE-like**: (1) Polyarthritis (2) Lymphadenopathy (3) Malar rash (4) Serositis (5) Leucopenia and/or thrombocytopenia **SSc-like**: (1) Sclerodactyly (2) Pulmonary fibrosis, restrictive changes, or reduced DLCO (3) Esophageal hypomotility or dilatation **PM/DM-like**: (1) Muscle weakness (2) Elevated CPK levels (3) Myogenic changes on EMG	*Requirements* Serological criterion present + ≥1 common symptom + ≥1 sign/symptom in at least two disease categories

anti-Sm anti-Smith, *DLCO* diffusion lung carbon monoxide, *SLE* systemic lupus erythematosus, *SSc* systemic sclerosis, *PM/DM* poly-/dermatomyositis, *EMG* electromyography, *RNP* ribonucleoprotein, *CPK* creatine phosphokinase

Table 8.5 Previously reported sensitivities and specificities of the aforementioned classification criteria

Classification criteria—year of publication	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Sharp's [9]—1987	42 [3] 57.7 [6] 70 [19] 76 [8] 100 [16]	38 [16] 87.7 [14] 90 [6]	58.6 [16]	100 [16]
Alarcón-Segovia's [10]—1987	62.5 [16] 69.4 [6] 91 [8] 100 [19]	86.2 [16] 99.4 [6]	71.4 [16]	80.6 [16]
Kahn's [11]—1991	52.3 [6] 62.5 [16] 85 [8]	86 [16] 99.4 [6]	71.4 [16]	80.6 [16]
Kasukawa's [12]—1987	56.2 [16] 75 [3] 77.5 [6] 92 [19] 94 [8] 96.2 [14]	65.5 [16] 92.2 [6] 99.8 [14]	47.4 [16]	73 [16]

Table 8.6 Tanaka's classification criteria for MCTD [13]

Common manifestations (1) Raynaud's phenomenon (2) Puffy fingers and/or swollen hands *Serological criterion* Anti-U1-RNP antibodies positivity (detected either by ELISA or double immunodiffusion) *Characteristic organ involvement* (1) Pulmonary arterial hypertension (2) Aseptic meningitis (3) Trigeminal neuropathy	*Mixed signs/symptoms* **SLE-like**: (1) Polyarthritis (2) Lymphadenopathy (3) Malar rash (4) Pericarditis or pleuritis (5) Leucopenia or thrombocytopenia **SSc-like**: (1) Sclerodactyly (2) Interstitial lung disease (3) Esophageal dysmotility or dilatation **PM/DM-like**: (1) Muscle weakness (2) Elevated CPK levels (3) Myogenic changes on EMG	*Requirements* ≥1 common manifestation + serological criterion present + ≥1 characteristic organ involvement OR ≥1 common manifestation + serological criterion present + ≥1 sign/symptom in at least two disease categories OR For children and adolescents only: ≥1 common manifestation + serological criterion present + ≥1 sign/symptom in at least one disease category

ELISA enzyme-linked immunosorbent assay. Notes: (1) When the result of double immunodiffusion is positive and inconsistent with that of ELISA, the result of double immunodiffusion supersedes that of ELISA. (2) When one of these antibodies is positive, the diagnosis of MCTD should be made with caution: (a) anti-dsDNA or anti-Sm, (b) anti-Scl-70 or anti-RNA polymerase III, (c) anti-aminoacyl-trasfer RNA synthetase or anti-melanoma differentiation-associated gene 5 (anti-MDA5). (3) Conditions in the differential diagnosis of each characteristic organ involvement (e.g., for aseptic meningitis: viral meningitis, drug-induced meningitis, and tumor-associated meningitis) should be excluded first

Tanaka's criteria were developed in 2019 by the Japanese Research Committee of the Ministry of Health, Labor, and Welfare [13]. Despite being somewhat similar to Kasukawa's criteria, a patient may be classified with MCTD if the following are present: at least one out of three "characteristic organ involvements" (pulmonary arterial hypertension, aseptic meningitis, and trigeminal neuropathy) plus positivity for anti-U1-RNP antibodies plus at least one common manifestation—the same as Kasukawa's. The authors reported a sensitivity and specificity of 90.6% and 98.4%, respectively. As of 2023, these criteria have never been studied outside of their validation cohort. Tanaka's criteria are summarized in Table 8.6.

Critical Analysis of the Classification Criteria

Establishing a correct diagnosis of MCTD in routine clinical practice is challenging since it may be hard to distinguish from CTDs such as SLE, SSc and PM/DM. In addition, even confirmed cases of MCTD at baseline may evolve into a more definite CTD during follow-up [5]. The most common misdiagnoses are SLE, non-MCTD overlap syndromes, UCTD, RA, and SSc [8].

It is evident that not only the diagnosis but also the classification of MCTD patients for research purposes presents several limitations [18]. For instance, up to 76% of patients fulfilling at least one set of MCTD criteria may simultaneously fulfill classification criteria of other CTDs, reflecting the overlap nature of this disease. Furthermore, only about 60% of patients fulfill all sets of MCTD criteria [8]; this may be related to conceptual differences among the sets of classification criteria, which may not capture the same patients even within the same MCTD clinical population [5]. Moreover, the employment of certain MCTD criteria in some studies but not in others may cause discrepancies among data arising from different cohorts [2]. Therefore, the lack of universally accepted classification criteria for MCTD may have a negative impact on the quality and quantity of studies on MCTD—and thus, on the publication of comparable data [5].

As previously given in Table 8.5, the reported sensitivity and specificity within each set of classification criteria vary among studies; this holds true especially for Sharp's and Kasukawa's criteria. To date, no studies have addressed this issue. Two studies recommended the use of Alarcón-Segovia's and Kahn's criteria to rule in MCTD due to their high specificity [6, 16]; by contrast, they were discordant on the sensitivity of Kasukawa's criteria, with only one of the studies [6] suggesting their potential role as a screening tool to rule out MCTD.

Tanaka's criteria are the most recently developed classification criteria for MCTD. Their peculiarity is the presence of a so-called characteristic organ involvement (trigeminal neuropathy, aseptic meningitis, and pulmonary artery hypertension) among the criteria. According to these criteria, it would be possible to classify a patient with MCTD when Raynaud's phenomenon (or puffy fingers), anti-U1-RNP antibodies, and one among trigeminal neuropathy, aseptic meningitis or pulmonary artery hypertension are present, even in the absence of overlapping manifestations. The authors themselves explicitly stated that these criteria may not be based on sufficient scientific evidence [13]. Moreover, they were validated only on a cohort of 51 patients, and therefore validation in other series of patients would be appropriate before their extensive use in clinical practice and research.

Despite being perhaps the most complete in terms of MCTD manifestations, Sharp's criteria require a large amount of data and thus are often regarded as highly complex in comparison with other sets of criteria, limiting their use in clinical practice and research [5]. As previously mentioned, anti-Sm antibodies represent an exclusion criterion for MCTD according to Sharp. While some claimed that this may confer more reliability to this set of criteria due to the high specificity of anti-Sm antibodies for SLE [17], others stated that anti-Sm antibodies can be present in MCTD and should not preclude MCTD classification [14]. One recent study specified that anti-Sm as well as anti-dsDNA antibodies may be only transiently positive in MCTD, and their persistence should strongly suggest a diagnosis of SLE [6]. Tanaka's criteria also suggested that a patient should be cautiously classified with MCTD if anti-Sm antibodies are present [13]. Further studies are warranted to clarify this issue.

Therapy and Prognosis

In 1972, Sharp et al. assumed that MCTD was a mild entity responsive to low-dose glucocorticoid therapy and with favorable outcome [1]. However, this observation has not been confirmed in the following decades. No randomized controlled trials of therapies for MCTD have been performed, and thus treatment decisions for MCTD are driven by experience from treating individual manifestations of SLE, SSc, RA, and PM/DM. Hydroxychloroquine is the basic immunomodulating treatment for MCTD. Immunosuppressive therapy includes glucocorticoids, methotrexate, cyclosporine, azathioprine, mycophenolate mofetil, and cyclophosphamide. Therapeutic strategies are often guided by the dominant clinical manifestation in MCTD. Symptomatic treatment of Raynaud's phenomenon consists of lifestyle changes (e.g., avoiding caffeine and cold temperatures), oral calcium channel blockers, intravenous prostanoids, and phosphodiesterase type 5 inhibitors. In the presence of digital ulcers, treatment includes endothelin receptor antagonists such as bosentan [5]. Biological drugs have been used with little experience and include rituximab, abatacept, tocilizumab, and Janus Kinase (JAK) inhibitors [5]. Pulmonary artery hypertension (PAH) is the main complication and cause of death in MCTD, followed by interstitial lung disease, infections, and acute cardiovascular events due to accelerated atherosclerosis [7]. PAH treatment strategies consist of double or triple therapy combinations including endothelin receptor antagonists, intravenous prostanoids, phosphodiesterase type 5 inhibitors, and selexipag [5]. The INBUILD trial showed that nintedanib, an intracellular inhibitor of tyrosine kinases, is effective against progressive lung fibrosis also in MCTD patients with ILD [20]. A prospective study of 280 patients found a survival rate of 98% at 5 years, 96% at 10 years, and 88% at 15 years; secondary antiphospholipid antibodies syndrome, malignancy and serositis were significantly more frequent in deceased patients [7].

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9

Relapsing Polychondritis

Philippe Mertz and Laurent Arnaud

Abstract

Relapsing polychondritis (RP) is a rare inflammatory disease characterized by recurrent episodes of inflammation of the auricular, nasal, and tracheal cartilage and a broad spectrum of systemic manifestations. The diagnosis of RP is based on the presence of typical chondritis, which may be lacking in up to 40% of cases at disease onset. Three main clinical phenotypes of RP have been described, each characterized by specific manifestations and the need for specific therapeutic management and follow-up. Screening for UBA1 mutations in the VEXAS syndrome (Vacuoles, Enzyme E1, X-linked, Autoinflammatory, Somatic) is essential in male patients over 50 years of age with macrocytic anemia, especially in the presence of dermatological, pulmonary, or thromboembolic manifestations. A thorough initial assessment is important to exclude the main differential diagnoses of RP (such as ANCA-associated vasculitis) and to search for another autoimmune or inflammatory disease, which is associated with RP in 20–30% of cases. Screening for tracheobronchial involvement is key, as respiratory manifestations are responsible for most of the morbidity and mortality of the disease. The therapeutic management of RP is not formally codified, and depends on the extent and severity of the disease.

Keywords

Relapsing polychondritis · Chondritis · Autoimmune · Criteria · VEXAS · Trachea · Deformities · Damage · Myelodysplasia

Introduction

Relapsing polychondritis (RP) is a rare inflammatory disease characterized by recurrent inflammation of cartilaginous structures, mainly of the ears, nose, respiratory tract and joints, isolated or together with a broad spectrum of systemic manifestations. Recurrent episodes of cartilage inflammation may lead to progressive loss of structural integrity with significant cosmetic complications.

Recently, efforts have been made to reclassify the phenotypic heterogeneity of RP into clinical subgroups based on organ-system involvement (minor chondritis, respiratory, and hematological subsets). These different clusters have distinct evolutive profiles and outcomes. Despite these advances, the challenge of defining effective treatments remains due to the rarity of the disease.

Epidemiology

The epidemiology of RP is not well understood, and there is currently no available national or international registry. The incidence ranges from 0.71 to 3.5 cases per million per year and the prevalence from 4.5 to 25 cases per million. Disease onset occurs typically around the age of 40 years, with an almost 1:1 sex-ratio [1–3]. Very rare pediatric cases have been reported [4]. In a British series, the standardized mortality ratio was 2.16 (95%CI: 1.24–3.51), with respiratory and cardiac complications, as well as cancer reported as the main causes of death [1]. According to a recent Japanese study [5], mortality from the disease has decreased from 9.2% in 2009 to 1.6% in 2019, possibly as a result of the more frequent use of biologics, especially in cases with tracheal involvement.

In 30% of cases, RP is associated with another autoimmune or inflammatory disease, which should be investigated thoroughly. In addition, a specific presentation, termed VEXAS-relapsing polychondritis (VEXAS-RP) has recently been described [6] and is important to recognize because of

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its association with mainly myelodysplastic syndrome and poorer prognosis.

Pathogenesis

The pathogenesis of RP is poorly understood. The disease is genetically associated with certain HLA alleles, but the search for these risk alleles is not of interest in current practice. Cartilage damage in chondritis results from an inflammatory infiltrate with autoreactive T lymphocytes targeting specific cartilage antigens and mono-macrophages as evidenced by high serum concentrations of monocyte chemoattractant protein-1 beta (MCP-1), macrophage inflammatory protein-1 beta (MIP-1-beta), and interleukin-8 (IL-8). Several autoantibodies (such as against collagen type 2, matrillin-1, and Cartilage oligomeric matrix protein) have been identified, but their low sensitivity advocates against routine testing [7]. Finally, the phenotype of RP in men over 50 associated with hemopathies, particularly myelodysplastic syndrome (VEXAS, Vacuoles, Enzyme E1, X-linked, Autoinflammatory, Somatic), has a distinct pathophysiology that will be discussed later.

Clinical manifestations

A better understanding of RP in recent years has allowed the identification of distinct phenotypes distinguished by varying organ involvement, consequently influencing prognosis and treatment strategies. Dion et al. retrospectively analyzed a French cohort of 142 patients with RP over a period of 12 years and described 3 main phenotypes using cluster analysis [2]: the most frequent phenotype (65%) was mainly characterized by episodes of recurrent chondritis of the ears and/or of the nose, the second cluster (≈25%) was characterized by respiratory involvement, and the third (≈10%) by hematological manifestations (recently associated with the VEXAS syndrome in most cases [6, 8–10]).

Mild relapsing chondritis phenotype

In 65% of cases, RP presents in its suggestive clinical form of auricular and nasal chondritis. The diagnosis is relatively straightforward once the main differential diagnoses have been ruled out.

Ear chondritis is the most common and suggestive symptom of the disease (affecting up to 90% of patients over the course of the disease); it may be unilateral or bilateral and involves inflammation of the cartilage part of the ear, sparing the non-cartilaginous lobule; this is an essential point of differentiation from other inflammatory ear diseases, particularly infections. The typical duration ranges from a few days to 1 or 2 weeks and resolves spontaneously. In case of recurrent episodes, a typical "cauliflower" appearance may develop.

Nasal chondritis is seen in up to 60% of patients and is characterized by pain at the junction between the nasal bone and the cartilage at the root of the nose. Repeated attacks may lead to the characteristic but non-specific "saddle nose" deformity.

Tracheo-bronchial Chondritis Phenotype

This cluster is characterized by chondritis of the tracheobronchial tree. This is one of the most severe forms of the disease and can be life-threatening. Laryngeal involvement (40% of patients) typically manifests as a dry cough, dysphonia, anterior cervical pain that might be aggravated by palpation of superficial cartilaginous structures as well as laryngeal dyspnea and stridor in case of subglottic stenosis.

Tracheobronchial involvement is potentially one of the most severe RP manifestations and should be systematically searched for when RP is suspected. Damage may result in tracheobronchial collapse and/or stenosis of the tracheal lumen, leading to respiratory failure. A unique feature of this condition is that the membranous posterior wall of the tracheobronchial tree is usually spared, except in advanced forms where the thickening may be circumferential. Very advanced forms may require tracheal stenting or reconstructive surgery.

Phenotype associated with myelodysplastic syndrome: VEXAS-RP

VEXAS syndrome (Vacuoles, E1 enzyme, X linked, Autoinflammatory, Somatic) is a recently described autoinflammatory disorder resulting from somatic mutations in the *UBA1* gene [6]. The disease leads to myeloid-driven systemic inflammation and bone marrow failure. Patients previously diagnosed with various inflammatory diseases resistant to standard therapies are now frequently recognized as having VEXAS syndrome, with associations to RP being actively studied. Ferrada et al. [9] detected a VEXAS mutation in 7.6% of 92 RP patients of the NIH cohort. These patients presented with a less severe cartilage involvement, without any cartilaginous damage or involvement of the large airways, and commonly presented with an infiltrative inflammatory disease of the lungs and thrombo-embolic complications. These findings were confirmed by Khitri et al. [10] who compared clinical characteristics between

VEXAS-RP and idiopathic RP in a retrospective French cohort, and found a greater prevalence of fever and higher median C-reactive protein levels, with a higher prevalence of ocular involvement, skin lesions, pulmonary infiltrates, and heart involvement in those with VEXAS-RP. In both studies, the prognosis was more often grieved by a refractory course to standard RP therapy. Screening for UBA1 mutations should strongly be considered if the RP patient is male and has an MCV >100 fL or platelet count <200,000/μL.

It is also important to consider that there are cases of RP associated with hematological abnormalities without evidence of a *UBA1* mutation (probably related to other somatic mutations yet to be discovered).

Particular phenotype: MAGIC Syndrome

Mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome is a rare disorder characterized by overlapping symptoms of RP and Behçet's disease (BD). Its classification as a distinct disease or an overlap syndrome remains controversial due to the lack of a well-defined definition. A study by Luo et al. [11] identified 13 of 96 RP patients in the NIH cohort with MAGIC syndrome. Notably, the VEXAS-RP patients did not overlap with those with MAGIC syndrome.

Of note, most patients with MAGIC syndrome are female (70%), and the median age at diagnosis is around 40 years. Compared to RP, MAGIC syndrome has a higher prevalence of mucocutaneous ulcers, inflammatory eye disease, BD-related cutaneous manifestations, venous thromboembolism, aortitis, gastrointestinal problems, and CNS involvement. Raynaud's phenomenon also emerges as a potential feature. The authors proposed a definition of MAGIC syndrome based on meeting both the McAdams or Damiani criteria for RP and the International Criteria for Behçet's Disease (ICBD) criteria for BD, resulting in high sensitivity and specificity. Validation of this definition in prospective studies may reduce diagnostic delays for MAGIC syndrome, a subset within RP that may be under-recognized by clinicians.

Other manifestations

Other organ involvement in RP is less common and is summarized in Table 9.1. The presence of neurological involvement, especially peripheral (which is exceptional), or renal involvement should systematically raise suspicion for the differential diagnosis of ANCA-associated vasculitis.

Table 9.1 Main clinical signs and symptoms

General signs	Fatigue, fever (VEXAS)
ENT and respiratory manifestations	Auricular and nasal chondritis Conductive deafness due to collapse of the cartilage of the external auditory canal Sensorineural deafness due to cochlear damage Vestibular syndrome Tracheobronchial or laryngeal chondritis Dysphonia Parenchymal infiltration (VEXAS)
Chondro-articular manifestations	Chondroarticular manifestations Sternocostal chondritis Inflammatory polyarthralgia Immunonegative oligo/polyarthritis SA-like axial involvement
Hematological manifestations	Macrocytic anemia suggestive of myelodysplastic syndrome (VEXAS)
Ophthalmological manifestations	Episcleritis Anterior scleritis, which may be complicated by scleromalacia or even perforation of the sclera
Cardiovascular manifestations	Aortic insufficiency due to dilatation of the aortic ring; aneurysm of the ascending thoracic aorta Pericarditis Conduction or rhythm disorders Thromboembolic manifestations (VEXAS)
Cutaneous manifestations	Multiple, non-specific (more frequent in cases of VEXAS)
Neurological manifestations	Rare, mainly central: meningitis and meningoencephalitis, usually lymphocytic, optic neuritis, cranial nerve damage, limbic encephalitis, etc. Peripheral neuropathy, exceptional: suggestive of AAV
Renal manifestations	Unusual: suggests ANCA-associated vasculitis

ANCA anti-neutrophil cytoplasmic antibody; *VEXAS* Vacuoles, Enzyme E1, X-linked, autoinflammatory, Somatic; *SA* spondyloarthritis

Laboratory features

The diagnosis of RP remains clinical as there are no distinctive laboratory markers. Routine laboratory tests can help assess organ involvement, track initial organ impairment, and monitor complications of treatment.

Biological tests may reveal an inflammatory syndrome (particularly elevated CRP), but this may be absent in up to 40% of RP patients. On the other hand, raised CRP is constant in VEXAS.

An important role of the initial laboratory workup is mainly to rule out differential diagnoses (especially ANCA-associated vasculitis).

Pathological features

Auricular biopsy is of limited value in routine assessment as no pathological finding is specific for RP. Yet, cartilage biopsy may be useful in certain circumstances, for example in patients with strictly unilateral auricular symptoms, lack of systemic involvement, and/or poor response to steroids, primarily to exclude a differential diagnosis. Immunofluorescence studies may show the presence of immunoglobulins and C3 deposits along the chondrofibrous junction and in the perichondral vessel walls.

Diagnostic criteria

The diagnosis of RP is based on a number of evocative clinical elements. Cartilage biopsy is not routinely performed because it is invasive and does not provide relevant diagnostic information. Several sets of diagnostic criteria [12–14] have been published (see Table 9.2). However, these criteria are neither sensitive nor specific and are therefore of limited clinical value.

Criticism on the diagnostic criteria

These diagnostic criteria, although valuable, have not been formally validated:

1. These criteria are based on empirical definition of RP based on the personal experience of the authors, without international expert input or consensus.
2. Given the rarity of the disease, no formal statistical comparison to other groups of patients has been performed to validate these classification criteria.

Furthermore, these criteria do not take into account the overlap with MAGIC syndrome or the recently described VEXAS-RP, which may have similar presentations.

Recommended initial assessment for any suspected RP case

The recommended initial assessment for RP is detailed in Table 9.3. It is important to identify associated autoimmune or inflammatory diseases (up to 30% of cases) (Table 9.4) and to make an initial mapping of organ involvement.

Table 9.2 Diagnostic criteria for relapsing polychondritis

McAdam et al. [12]	Damiani and Levine [13]	Michet et al. [14]
1. Recurrent chondritis of both auricles 2. Nonerosive inflammatory polyarthritis 3. Chondritis of nasal cartilage 4. Inflammation of ocular structures including conjunctivitis, keratitis, scleritis/episcleritis, and uveitis 5. Chondritis of the respiratory tract involving laryngeal and tracheal cartilages 6. Cochlear or vestibular damage manifested by neurosensory hearing loss, tinnitus, and vertigo **Three of the six criteria are necessary for diagnosis** **Biopsy is not essential for diagnosis**	Similar as McAdam 1. At least three of McAdam's criteria 2. One or more of McAdam's criteria and positive histology 3. Chondritis in two or more separate anatomical locations with response to steroids and/or dapsone	Major criteria: • Proven inflammatory episodes involving auricular cartilage • Proven inflammatory episodes involving nasal cartilage • Proven inflammatory episodes involving laryngotracheal cartilage Minor criteria: • Ocular inflammation • Hearing loss • Vestibular dysfunction • Seronegative inflammatory arthritis **Diagnosis if 2 major criteria or 1 major criteria plus 2 minor criteria** **Biopsy is not essential for diagnosis**

Table 9.3 Recommended initial assessment

Biological examinations
– **Standard laboratory work-up** – **Hemogram:** anemia or macrocytosis suggestive of VEXAS syndrome – Raised **acute phase reactants** (absent in 40% of attacks) – **Immunological work-up to rule out a differential diagnosis:** anti-nuclear antibodies, anti-ENA, rheumatoid factor and anti-CCP factors, ANCA, etc.
Suggested investigations
– **Dynamic cervicothoracic CT scan, when possible with two- or three-dimensional reconstruction:** evaluation of the larynx and tracheobronchial tree for specific damage and/or its sequelae, search for lung parenchymal damage suggestive of VEXAS syndrome – **TTE:** to look for associated valvulopathy and dilatation of the ascending aorta – **EKG:** look for conduction or rhythm disorders – **Functional respiratory tests:** look for functional repercussions of possible laryngotracheobronchial damage
Suspected VEXAS syndrome
– **Search for *UBA1* mutation preferably on bone marrow,** otherwise peripheral blood (lower sensitivity reported)
Tests not recommended in routine practice
– **Cartilage biopsy** – **HLA typing, search for anti-collagen type 2 or anti-matrillin 1 antibodies**

ANCA: neutrophil cytoplasmic antibody; CCP: cyclic citrullinated peptide; DLCO: diffusion capacity of carbon monoxide; ECG: electrocardiogram; ENA: extractable nuclear antigen; TTE: trans-thoracic echocardiography; HLA: human leukocyte antigen; CT: computed tomography; VEXAS: Vacuoles, Enzyme E1, X-linked, Autoinflammatory, Somatic

Table 9.4 Main autoimmune/inflammatory diseases associated with RP

Autoimmune diseases	Sjögren's syndrome Systemic lupus Antiphospholipid antibody syndrome Mixed connective tissue disease Rheumatoid arthritis Hashimoto's thyroiditis Type 1 diabetes Primary biliary cirrhosis Myasthenia
Inflammatory diseases	Spondyloarthritis Behçet's disease and MAGIC syndrome Inflammatory bowel disease (IBD)
Others	Non-*UBA1* myelodysplastic syndrome Lymphoma Monoclonal gammopathy

Differential diagnosis and common associations

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), particularly proteinase 3 (PR3)-associated granulomatosis with polyangiitis (GPA), is one of the major differential diagnoses. The presence of these antibodies excludes RP as a diagnosis. An important differentiating factor between RP and AAV is renal involvement, which is common in AAV and remains controversial in the context of RP.

Prognosis

RP is a disease which most commonly occurs in the form of relapses of unpredictable frequency and severity. Symptom persistence between attacks is common. The three RP phenotypes necessitate distinct therapeutic approaches due to varying prognosis. Systematic investigation for tracheobronchial involvement is vital, as respiratory involvement contributes significantly to morbidity and mortality. In males over 50 with macrocytic anemia, VEXAS syndrome assessment is crucial, particularly in case of dermatological, pulmonary, or thromboembolic features. Adverse prognostic indicators include male gender, cardiovascular disease, and VEXAS syndrome.

RP often leads to significant functional repercussions such as hearing loss, balance issues, vision impairment, and persistent pain.

Treatment of relapsing polychondritis

Given the rarity of RP and the lack of randomized trials, standardization of treatment remains a challenge. Apart from recent French guidelines of FAI2R [15] and selected guidelines from ERN ReCONNET [16], there are no formal official recommendations. The main goals of treatment are to control disease activity, prevent damage and avoid treatment-related complications. Management ranges from symptomatic treatment (non-steroidal anti-inflammatory drugs [NSAIDs] and analgesics) to steroids and other immunosuppressants (conventional and biological disease-modifying antirheumatic drugs) in case of severe or refractory disease. Some cases require continuous glucocorticoid background therapy to reduce flare frequency.

A recent comprehensive literature analysis [17] synthesized findings from approximately 250 distinct treatment regimens and indicated that abatacept (pooled response rate: 72% [95% CI: 42–95]), tocilizumab (64% [95% CI: 53–74]), TNFi (such as infliximab, 59% [95% CI: 42–75]), anakinra (47% [95% CI: 26–68]), and rituximab (43% [95% CI: 20–68]) could be considered in refractory cases.

VEXAS-RP patients exhibit comparable steroid dependency rates to idiopathic RP, with similar usage of cDMARDs and bDMARDs [10]. Notably, tocilizumab stands out for its substantial efficacy and extensive case utilization. In VEXAS-RP, a distinctive approach involves azacytidine, a DNA methylation inhibitor from MDS treatment, which may prove useful for high cortico-dependency, multi-refractory cases, or severe underlying MDS [18]. Allogeneic stem cell transplantation may be considered if azacytidine proves insufficient.

Disease and damage monitoring

In 2012, Arnaud et al. [19] collaborated with an international panel to develop the Relapsing Polychondritis Disease Activity Index (RPDAI), comprising 27 elements with specific weights. In a recent study, Cao et al. found a positive correlation between RPDAI and three inflammation markers (C-reactive protein to albumin ratio, neutrophil to lymphocyte ratio, and platelet to lymphocyte ratio) in 170 RP patients.

Distinguishing disease activity from damage proves challenging in routine practice, especially in RP. In 2018, Mertz et al. developed the Relapsing Polychondritis Damage Index (RPDAM), developed with an international multidisciplinary team of experienced professionals [20]. RPDAM comprises 17 items encompassing disease-specific and treatment-related damage. However, RPDAM is currently pending formal clinical validation.

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Raynaud's Phenomenon (RP)

10

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Abstract

Due to vascular compromise, Raynaud's phenomenon (RP) is a reversible vasospastic phenomenon. It can be a primary, idiopathic, or secondary (Raynaud syndrome) and is associated with an underlying disease, usually autoimmune. The symptoms, ranging from mild discomfort to severe pain, can eventually lead to ulcerations, tissue necrosis, and gangrene due to vascular disease. Currently, various studies have shown the role of the endothelium and endothelium-independent mechanisms in the altered vasoregulation of Raynaud's phenomenon.

The clinic makes the RP diagnosis and must differentiate between primary or secondary Raynaud's phenomenon. The treatment of this vasculopathy is initially by avoiding the triggers. In case of no improvement or complications, pharmacological treatment is carried out that is based on the reduction of vasoconstriction and the increase in blood flow. Prognosis depends on the underlying disease.

Keywords

Raynaud's phenomenon · Pathophysiology · Endothelium · Vasospasm

Introduction

Raynaud's phenomenon (RP) is a vascular event triggered by cold or emotional stress, usually symmetric and reversible in the skin, and causes a triphasic color change in three different phases: white (ischemia), blue (cyanotic phase), and red (reperfusion). RP can be primary (idiopathic) or secondary. When these symptoms are present with no underlying cause demonstrated, it is called "primary RP" (PRP). When there is an underlying disease, most often rheumatic, hematological, and vascular disease, is called "secondary RP" (SRP). RP can have different intensities, from being a reversible vasospasm only triggered by extremely cold to progressive obliterative microangiopathy, which is frequently associated with systemic sclerosis (SSc) [1].

Epidemiology

RP is more common and prevalent among inhabitants in cold climates than in tropical ones. RP affects approximately 5% of the world population and differs depending on whether it is primary or secondary. RP could be present in SSc in almost 100% of the patients. RP has been described in children and the elderly and has a worldwide distribution. Women are the most affected, with a female-to-male ratio of 9 to 1.

The lowest prevalence has been reported in Japan (2.1% in women, 1.1% in men) and the highest in northern Sweden (14.5% in women, 12.7% in men) [2]. The average age of onset is 31 years for women and 35 years for men; more than 75% of patients begin having symptoms before 40 years old.

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Classification

PRP is fully reversible and episodic, and frequently cold triggered, objective microvascular imaging has no structural change, and serological studies are typically negative [1]. The term SRP comprehends a broad range of different diseases. (See Table 10.1.)

Many risk factors have been described for PRP, like female gender, colder climate, low weight, smoking, manual occupation, and atherosclerotic diseases; alcohol consumption in women is associated with an increased risk of RP, but moderate alcohol consumption in men is associated with reduced risk [3].

In SSc, the symptoms of RP are often the first clinical manifestation and predate other clinical features by several years. RP is characteristic of SSc and occurs in >96% of patients, while it is lower in systemic lupus erythematosus (SLE) (30%), primary Sjogren's syndrome (30%), and inflammatory myopathies (40%).

Table 10.1 Causes of SRP [3]

Connective tissue diseases	Systemic sclerosis CREST syndrome MCTD SLE Sjogren's syndrome Dermatomyositis
Drugs and toxic agents	β-blockers (including those in ocular solutions) Ergot derivatives Cancer chemotherapy Cyclosporine Interferons α and β Vinyl polychloride Cocaine Smoking
Endocrine disorders	Hypothyroidism Pheochromocytoma Carcinoid syndrome
Trauma	Vibration injury Ulnar aneurysm (hypothenar hammer syndrome) Repetitive stress injury (thoracic outlet syndrome)
Hematological disorders and cancer	Cryoglobulinemia Cold agglutinin disease Myeloproliferative and lymphoproliferative disorders
Arterial disease	Thromboangiitis obliterans Peripheral embolism Vasculitis (giant-cell arteritis, Takayasu)

MCTD mixed connective tissue disease, *SLE* systemic lupus erythematosus. (Adapted from Hirschi et al. [3])

Pathogenesis

RP is due to an imbalance of function of the small blood vessel, which alters vasodilator and vasoconstrictor responses by alterations in neural control, vascular tone, and circulating mediators. Physiological normal regulation of peripheral blood flow depends on several factors: intrinsic vascular tone, sympathetic nervous activity, circulating neurohumoral substances, and blood viscosity. The pathogenesis and pathophysiology of SRP depend on underlying conditions.

Genetic factors play an essential role in PRP. First-degree relatives of patients with RP have up to a 50% risk of presenting this phenomenon. Therefore, we can assume that genetic alterations may be related. Variation in genes encoding some ion channels (e.g., TRP [transient receptor potential] M8) or vasoactive agents (e.g., nitric oxide [NO]) may be expected to result in the RP phenotype. Other alterations have been described in the single nucleotide polymorphisms (SNPs) in genes TRPA1, TRPM8, CALCA, CALCB, and NOS1 [4].

Other substances have been described in the pathogenesis of RP. It has also been described that the renin-angiotensin system (RAS) has a role in vascular tone even in oxidative stress and has a significative role in remodeling. In SRP, the full effect is unknown. Although it has been described that the RAS in these patients is elevated and could be a window of opportunity in treatment using inhibitors of angiotensin receptors. There are also increased circulating levels of endothelin-1, which has a vasoconstrictor effect and is involved in fibrosis and structural-vascular changes, so inhibition of endothelin-1 receptors might affect vascular remodeling proliferation of smooth-muscle cells and fibroblasts and could be a possible treatment target in patients with SRP due to SSc [5].

In the pathogenesis of SRP, the mechanisms postulated concerning vascular abnormalities in structure and function, increased sympathetic nervous system activity, high digital vascular reactivity to vasoconstrictive stimuli, several circulating vasoactive hormones, and decreased intravascular pressure. Intravascular abnormalities have been described, including platelet activation, impaired fibrinolysis, increased viscosity, and oxidant stress.

Changes in blood flow maintain thermoregulation [6]. The local cooling of the skin causes vasoconstriction, triggering TRP channels and the release of neuropeptide Y, calcitonin gene-related peptide, and vasoactive intestinal polypeptide from sensory nerves. There are also proteins, such as TRPM8, a thermosensitive ion channel, in response to cold and cold mimetic substances expressed in sensory neurons [7].

Also, in the skin of the fingers, low-resistance arteriovenous anastomoses (AVA) allow high blood flow from arterioles to veins to provide nutrition to the skin. The sympathetic tone with the release of norepinephrine decreases blood flow. In healthy people, the blood flow reduces with cold exposure in the arteriovenous anastomoses, but the nutritional flow remains intact. Although in patients with SRP, the reduction of flow decreases nutritional flow. When vascular smooth muscle is exposed to cold, the α-2-adrenergic receptors release norepinephrine, which causes vasoconstriction [8].

Various studies have shown that β agonists increase peripheral blood flow, while β blockers potentiate exogenous vasoconstriction in the vessels. In SRP, repeated vasoconstriction causes endothelial damage from ischemia-reperfusion injury due to the release of free radicals, endothelin, 5-hydroxytryptamine, and thromboxane and decreases the NO, resulting in vasospasm. Moreover, prostaglandins increase fibrinolytic activity [9], this damage is associated with structural deterioration and loss of the cutaneous vessels, including the nutritional microvasculature [10]. In SSc vasculopathy, there exists a reduction of the luminal diameter by vascular remodeling, including intimal and smooth muscle hypertrophy.

Due to therapeutic intervention, knowledge of the mechanisms implicated in the pathogenesis of secondary RP is important. For example, if the RP is due to hematological disease, which increases plasma viscosity, the treatment will be aimed at reducing it rather than reducing vasoconstriction.

Clinical Manifestations

The symptoms of RP depend on the severity of the vasoconstriction, and it is triggered by cold stimuli or emotional stress. Attacks of RP commonly affect the digital extremities, including the fingers and toes, but other vascular beds, including the nose, ears, lips, and nipple, have been described. All the fingers of the hand can be affected, but the involvement of the thumb can be the first sign of an underlying autoimmune disease.

Classically, RP has three phases; the first one is white, secondary to vasoconstriction or occlusion of the precapillary arterioles; the second one could be blue or purple (cyanosis) and is secondary to deoxygenation of sequestered blood following vasoconstriction/occlusion of the postcapillary venules, and finally red (post-ischemic hyperemia) due to reperfusion. At least half of the patients will exhibit the three phases, and the rest will develop one or two phases [11]. The intensity of the vasoconstriction and its duration are proportional to the severity of the symptoms. In addition to the digital color changes, these patients are frequently associated with paresthesia, numbness, and tingling that will disappear once the color returns to normal; they are usually not in pain at this time. It is essential to consider that acrocyanosis is often preferentially applied in vaso-occlusive disorders such as cold agglutinin. Cyanosis (without blanching) appears more often in SSc than among people with PRP, whereas reactive hyperemia seems less common in SSc. Cold-induced digital color changes focus on the reversible vasospastic aspects of RP. More persistent digital vascular compromise secondary to the irreversible and often progressive obliterative microangiopathy also contributes to digital vascular symptoms in SSc [12].

Most patients with mild disease notice skin discoloration only upon cold exposure. Patients with SRP can also have symptoms related to their underlying conditions. RP is the initial symptom in 70% of patients with scleroderma and other rheumatic diseases and is the most common presenting feature of SSc; approximately 95% of patients with SSc have RP.

However, presentation with RP should prompt a search for any connective tissue disease. This search involves a relevant history and careful clinical examination, especially of the hands. It is recommended that all patients presenting with RP should have their antinuclear antibody (ANA) tested, even in children. On the other hand, RP is one of the "red flags" of VEDOSS (Very Early Diagnosis of SSc); suspected secondary RP was defined by ANA positivity and capillary abnormalities. The mean incidence rate of transition from primary RP to a connective tissue disease was 2.65/100 patient-years (95% confidence interval [CI]). The transition rate from primary RP specifically to SSc was 0.93/100 patient-years (CI 95%) [13].

Pathological Features

The evaluation of RP includes several methods, such as video nailfold capillary microscopy (VNC). Therefore, it should be considered as the essential tool of investigation to distinguish primary from secondary RP. The capillaroscopic patterns found in patients with RP are variable; several studies have demonstrated that patients with PRP do not exhibit capillary nail fold changes. However, patients with autoimmune diseases like mixed connective tissue disease (MCTD), SSc, or inflammatory myopathies demonstrate capillary nailfold abnormalities. Some characteristics of VNC changes of SSc are the presence of giant capillaries, microhemorrhages, and avascular areas, and some of this could be present in other autoimmune disorders.

Other diagnostic tools can be used to differentiate a PRP from an SRP. Angiography could be used to exclude compressive or obstructive macrovascular diseases. Thermography, finger systolic pressure measurement, laser Doppler flowmetry, laser Doppler imaging, laser speckle contrast analysis, and plethysmography have been described. However, they are not yet standardized methods for routine use.

Diagnostic Criteria

The evaluation of patients with RP includes a clinical history, examination, laboratory investigations, and imaging studies, the physical examination and anamnesis should be focused on vascular symptoms, which include cold intolerance. The age of presentation may also support a clinical suspicion (between 15 and 25 years old for PRP). There may be other relevant historical clues (e.g., occupational exposure to vibrating tool use, recent weight loss, changes to drug therapy). SRP should be considered in people developing symptoms over the age of 30 years.

The identification of RP includes episodic attacks of acral pallor or cyanosis; no evidence of digital pitting, ulcerations, or gangrene; normal pattern NVC; negative ANA testing results; and normal erythrocyte sedimentation rate, rheumatoid factor, thyroid hormone levels, and protein levels to exclude associated rheumatic diseases and thyroid disorder. Commonly, most patients with PRP are women, and it is a rare loss of tissue or necrosis [1].

There is no single tool for the diagnosis of RP, the international consensus criteria for diagnosing RP in 2014, recommend using the three-step approach for diagnosing RP. The panel agreed that a normal ESR and a normal ANA were not required to diagnose PRP (see Table 10.2).

Besides, Maverakis et al. create diagnostic criteria for PRP, requiring a negative ANA or low titer ANA (e.g., 1:40 by indirect immunofluorescence [IFI]). However, a negative ANA with cytoplasmic stain could indicate the presence of anti-synthetase antibodies such as anti-Jo-1 or rarer SSc-specific autoantibodies such as anti-EIF2B. If clinical features warrant another laboratory testing, like creatinine kinase, complements, immunoglobulins with protein electrophoresis, and fasting lipid profile may be considered with suspicious clinical parts such as puffy fingers, involvement of the thumbs, gastroesophageal reflux, inflammatory arthralgia, mucocutaneous manifestations and digital ischemic lesions and other organ system involvement, including gastrointestinal, cardiopulmonary, or renal abnormalities and multi-organ system complications occurring frequently.

Differential Diagnosis

The differential diagnoses are summarized in Table 10.3.

Table 10.3 Differential diagnoses of RP [14]

Differential diagnosis of Raynaud's phenomenon	
Autoimmune, rheumatological	Rheumatoid arthritis, systemic lupus erythematosus, scleroderma, CREST syndrome, thromboangitis obliterans
Endocrine	Hypothyroidism
Hematological	Polycythemia
Musculoskeletal	Carpal tunnel syndrome, thoracic outlet syndrome
Others	Occupational (vibrating tools), drugs (chemotherapeutic agents, ergotamine, amphetamines, bromocriptine)

CREST: calcinosis, RP, alterations of the esophageal motility, sclerodactyly, and telangiectasia. (Taken from: Choi et al. [14])

Table 10.2 Three-step approach to diagnosis of RP. (Diagnosis of RP can be done if three or more criteria are met from Step 3) [1]

Step 1	
Ask screening question	Are your fingers unusually sensitive to cold? Proceed to Step 2 if the answer is "yes"
Step 2	
Assess color changes	Occurrence of biphasic color changes during the vasospastic episodes (white and blue)
Step 3	
Calculate disease score	(a) Episodes are triggered by things other than cold (e.g., emotional stressors) (b) Episodes involve both hands, even if the involvement is asynchronous and/or asymmetric (c) Episodes are accompanied by numbness and/or paresthesia (d) Observed color changes are often characterized by a well-demarcated border between affected and un-affected skin (e) Patient provided photograph(s), strongly support a diagnosis of RP (f) Episodes sometimes occur at other body sites (e.g., nose, ears, feet, and areolas) (g) Occurrence of triphasic color changes during the vasospastic episodes (white, blue, red)

Adapted version from the International Consensus Criteria for the Diagnosis of RP from Maverakis et al. [1]

Prognosis

The annual remission of RP varies between 3% and 9% depending on the geographic region. Meanwhile 13% of RP patients developed a secondary disorder, many of which are autoimmune diseases. The patients evaluated for differences between PRP or SRP in whom NVC and specific autoantibodies found microvascular damage had a 79% probability of developing definitive SSc after up to 9 years of follow-up [2].

Impact of RP on Health-Related Quality of Life

The quality of life is not diminished by RP of moderate intensity, and the intensity of the symptoms improves with lifestyle changes like cold avoidance in most PRP. Vasodilator therapy should be used, and in case of being secondary to rheumatic diseases add immunosuppressive therapies whether symptoms persist [14].

Treatment

Raynaud's phenomenon management aims to avoid complications caused by decreased blood flow and the release of mediators of endothelial damage caused by vasoconstriction.

Nonpharmacological Interventions

General indications should be applied to all patients with RP. The temperature must be maintained with different layers of clothing, as well as avoiding smoking, emotional stress, and tools that vibrate the hand may reduce the frequency of attacks. Patients with RP should avoid medications that can aggravate blood vessel spasms, such as ergotamine derivates, beta-blockers, amphetamines, and sumatriptan. Some authors recommend that fish oils containing omega-3 fatty acids may benefit some patients with PRP, and in some cases, the addition of aspirin or clopidogrel is prescribed to decrease the risk of thrombotic complications in all cases of RP [15].

Pharmacological Management

When SRP is present, the underlying pathology must first be treated [1]. The initial pharmacological treatment should be based on the reduction of vasomotion by use of vasodilators (nitrates, calcium-channel blockers, prostaglandins, PDE-V inhibitors) and inhibition of vasoconstriction (endothelin-receptor antagonists, angiotensin-receptor blockers, alpha-receptor blockers). Other substances that may improve symptoms of RP, improving endothelial function, are rho-kinase inhibitors and statins, and serotonin-reuptake inhibitors (fluoxetine), which work through interaction with neural vasoregulation.

Most patients with PRP are treated with general indications. Meanwhile, patients with SRP should be treated with pharmacological treatment.

Drug therapy is initiated when nonpharmacologic approaches are ineffective in reducing the severity of vasospastic attacks; pharmacological treatment should start with the lowest dose, increasing the dose due to no response to the vasospastic symptoms, avoiding adverse effects.

The most used drug class for the treatment of RP is calcium channel blocker (CCB), which relaxes smooth muscle and dilates the small blood vessels. A meta-analysis found that this type of treatment (nicardipine and nifedipine) reported a significant improvement in the symptoms (73% vs. 33% placebo) and the frequency of attacks and had the same improvement in patients with PRP or SRP. It has been described that nifedipine had a more significant effect on the severity of the attack than nicardipine; other CCBs don't have enough data to compare [16].

It has been shown that low doses of nifedipine or diltiazem have superseded topical or oral nitroglycerin for the treatment of vasospasm. The most frequent adverse effects are headache, dizziness, nausea, palpitations, and ankle edema; these side effects could be diminished by reducing the dose or changing to another CCB. Another treatment could be Prazosin, a postsynaptic 1-adrenergic antagonist that counteracts the actions of norepinephrine, a hormone that constricts blood vessels. Low-dose prazosin therapy reduced the number and duration of attacks and improved finger blood; another treatment could be sildenafil, which is a phosphodiesterase type 5 (PDE-5) inhibitor and has been shown to decrease the number of digital ulcers [17].

Nitrates increase perfusion at both distal and extensor digital ulcer cores and can be administered topically with good tolerance, a few side effects, and an important improvement in distal flow.

Even though angiotensin-converting enzymes and prostaglandins could be implicated in the pathophysiology of RP, using angiotensin-converting enzyme inhibitors or intravenous prostaglandins is still controversial [15].

Intravenous prostaglandins have also been used with success, such as iloprost, which, when given as a 5-day infusion, was beneficial in severe cases of RP; alprostadil (prostaglandin E_1 [PGE_1]) and epoprostenol (PGI_2) are considered as alternatives. Bosentan, an endothelin receptor antagonist, has been used to treat refractory SRP and digital ulcers, usu-

Table 10.4 Pharmacological treatment of RP

Agent	Dose	Side effects
Nifedipine	10–30 mg 3 times daily (PO)	Tachycardia, hypotension, palpitations, constipation, anxiety
Amlodipine	5–20 mg daily (PO)	
Diltiazem	30–120 mg 3 times daily (PO)	
Sildenafil	50–100 mg 2 times daily (PO)	Dizziness, headache, fatigue, hypotension
Losartan	25–100 mg daily (PO)	Dizziness, headache, fatigue, diarrhea
Prazosin	1–5 mg 2 times daily (PO)	Orthostatic hypotension, nausea, headache
Fluoxetine	20–40 mg daily (PO)	Insomnia, nausea, diarrhea, tremors
Pentoxifylline	400 mg 3 times daily (PO)	Dyspepsia, nausea, vomiting
Epoprostenol	0.5–6 ng/kg of body weight/min intravenously for 6–24 h, for 2–5 days	Diarrhea, headache, rash, hypotension
Iloprost	3–5 consecutive days every 6–8 weeks or 50–150 mg 2× daily (PO)	Headache, rash, hypotension
Nitroglycerin	10% gel, 6–8 h, starting 0.5 in Patch	

PO: orally. (Adapted from Pope et al. 2007)

ally in patients with scleroderma. It is recommended to start treatment with 125 mg daily for the first 4 weeks, followed by 125 mg twice daily. This dose has improved the ischemic lesions by healing digital ulcer patients during the first month of therapy. The pharmacological treatment of RP is summarized in Table 10.4.

Finally, the choice of pharmacological treatment depends on shared decision-making between the provider and the patient based on a discussion of the side-effect profile of each agent. In older patients, CCBs are preferred because they are common higher developing side effects to α1-adrenoceptor antagonists. In patients with secondary RP, CCBs, α1-adrenoceptor antagonists, or PDE-5 inhibitors are a reasonable first choice. Topical nitrate or intravenous prostacyclin can be added in patients with persistent digital ischemia or symptoms.

In some cases, surgery should be considered; sympathectomy is indicated for pure vasospastic disease refractory to medical management [5]. Recently, botulinum injection has been described into the perineurovascular tissue of the wrist, the distal palm, or along the digits, although currently is an off-label application, and only case series are reported [18].

Peripheral digital sympathectomy may have a role in treating people with complicated secondary RP and is recommended for a patient with intractable ischemic pain [19] and a high recurrence rate. Single-port thoracoscopic sympathectomy is a minimally invasive technique that improves hand perfusion and reduces the number of attacks. Another method is direct microsurgical revascularization by reversing a lesser saphenous vein graft and anastomosing this “end to side” to the radial artery with an improvement in the digital ischemia in the follow-up but only in case reports [20].

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11

Drug-Induced Autoimmunity

Martine Szyper-Kravitz, Yehuda Shoenfeld,
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Abstract

Drug-induced autoimmunity encompasses a wide range of serological and clinical manifestations that develop after exposure to a drug. The typical and most studied example is drug-induced lupus (DIL). Although autoimmunity secondary to drugs has been recognized for over 70 years, introducing new drugs has extended the spectrum and severity of clinical manifestations. Several drugs are associated with the induction of antinuclear and anti-DNA antibodies. Still, clinical lupus is rare, and several drugs are associated with antineutrophilic cytoplasmic antibody (ANCA)-positive vasculitis. Diagnosing these conditions is complex and requires carefully eliminating other possible conditions. Although rare cases of life-threatening autoimmune diseases have been described, most cases are mild and resolve after the offending drug is discontinued.

Keywords

Drug-induced · Idiosyncratic reactions · Drug-induced lupus

Drug-induced autoimmunity (D-IA) refers to the emergence of an autoimmune serological profile or an autoimmune condition after exposure to a drug. Most of the literature concerning drug-induced autoimmunity consists of case reports illustrating specific autoimmune disorders that developed in particular patients, and only a few controlled studies have been published. Some of the postulated mechanisms have been prospectively investigated in experimental models. The induction of autoantibodies following the introduction of tumor necrosis factor inhibitors (TNFi) in treating several diseases has provided a comprehensive database on the prevalence, clinical significance, and possible mechanisms for drug-induced autoimmunity; more recently, immunotherapy with checkpoint inhibitors has been associated with autoimmune-related adverse effects (irAEs). This chapter reviews current trends in drug-induced autoimmunity, including the postulated mechanisms, the range of autoimmune manifestations, and their clinical relevance.

Epidemiology

The possibility of D-IA was first raised in 1945 with a report of possible sulfadiazine-induced lupus, followed in 1953 by hydralazine being implicated in the induction of lupus. Since then, more than 100 drugs have been involved in drug-induced lupus (DIL) (See Table 11.1 for a list of drugs). For instance, procainamide-induced lupus is estimated to occur in approximately 20% of cases within the first year of therapy, while hydralazine-induced lupus has an incidence ranging from 5% to 8%. The emergence of biological modulators, such as tumor necrosis factor (TNF) inhibitors, has introduced new considerations [1]. The British Society for Rheumatology Biologics Register-RA database (BSRBR) reported a TNFi risk of 10 cases for every 10,000 people for DIL and 15 cases for 10,000 people for vasculitis-like events, with the highest events proved after infliximab [2]. The incidence and prevalence of other drug-induced autoimmune manifestations are not known.

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Table 11.1 Some drugs implicated in drug-induced autoimmunity

Antibiotics	Minocycline, isoniazid, cefuroxime, nalidixic acid, nitrofurantoin
Antifungals	Griseofulvin, voriconazole
Antiarrhythmics	Procainamide, quinidine, propafenone
Antihypertensives	Hydralazine, methyldopa, captopril, acebutolol, atenolol
Anticonvulsants	Valproate, carbamazepine, phenytoin, levetiracetam
Antipsychotics	Chlorpromazine
Anti-inflammatory	D-penicillamine, phenylbutazone, sulfasalazine
Cholesterol-lowering agents	Lovastatin, simvastatin, gemfibrozil
Antithyroid	Propylthiouracil, methimazole
Biologic agents	Anti-interleukin 2, interferon-α, β, γ, TNF-α inhibitors, anti-CD52, anti-interleukin 1

Pathogenesis

The disruption of immune control by D-IA leads to the breakdown of tolerance, affecting both central and peripheral mechanisms. Central tolerance, achieved through thymocyte deletion, and peripheral tolerance, upheld by various mechanisms, are susceptible to certain drugs. The occurrence of immune-related adverse events is influenced by individual predisposition, the specific drug used, and the duration of treatment [3]. In the context of procaine-induced lupus studies, procaine-hydroxylamine injections into mice's thymus resulted in chromatin-reactive T cells and IgG autoantibodies, breaking B-cell tolerance [4]. Notably, the drug's impact extends to preventing anergy induction and self-unresponsiveness during positive selection [4].

Drugs implicated in lupus induction, such as hydralazine and procainamide, disrupt T-cell DNA methylation, akin to the effects of UV light. Richardson's experiments illustrate that this disruption increases autoreactivity, leading to a lupus-like disease upon adoptive transfer [5]. Furthermore, DNA-hypomethylating drugs induce the overexpression of lymphocyte function-associated antigen 1 (LFA-1), a phenomenon observed in patients with systemic lupus erythematosus (SLE), underlining the clinical relevance of these findings [5].

A crucial aspect of D-IA involves the cross-reactivity of T cells with self-antigens. Drug-specific T-cell clones (TCCs) exhibit reactivity to alloantigens, suggesting the presence of broadly reactive T cells recognizing both the drug and HLA peptide alleles. This cross-reactivity disrupts tolerance, contributing to the emergence of autoimmunity [6].

The "hapten hypothesis" posits that drugs binding to proteins alter their recognition as "self," initiating intricate immune reactions. Antigen modification triggers inflammatory responses, playing a role in the development of adaptive immunity. Processes such as epitope spreading and altered antigen processing, exemplified by substances like gold, further contribute to immune responses [7, 8]. Reactive metabolites of drugs implicated in haptenization can be transferred by lymphocytes, adding another layer to the complexity of D-IA [9]. Additional mechanisms, including molecular mimicry and superantigen stimulation, further contribute to the facilitation of autoimmunity.

Clinical Manifestations

Drug-induced autoimmunity may manifest in diverse clinical manifestations, ranging from organ-restricted to systemic diseases. In the most studied case of DIL, induced by procainamide and hydralazine, the condition is characterized by arthralgia, myalgia, pleurisy, rash, and fever. In contrast, pericardial, central nervous system (CNS), and renal involvement is rare. Oral ulcers, alopecia, and photosensitivity, typical in SLE, are occasional in these cases of DIL, but purpura and erythema nodosum are more prevalent. In patients treated for more than a year with procainamide, 20% are at risk for developing symptoms compared to 5–8% among hydralazine-treated patients [10]. To date, the therapeutic use of procainamide and hydralazine has declined dramatically, and most cases of DIL are induced by other new drugs, changing the classical presentation of DIL (resembling more idiopathic SLE) and expanding the spectrum to new autoimmune manifestations.

In cases of antiphospholipid syndrome (APS) induced by drugs such as chlorpromazine, a low frequency of thrombosis, <6% during 5 years of follow-up, has been reported, as compared with a 56–87% prevalence of antiphospholipid antibodies [10].

The Rasmussen et al. research using the French pharmacovigilance database (FPVD) found 115 cases of drug-induced IgA vasculitis of the 467 cases presented in children and adult populations. The most frequent drugs associated were vaccines, antibiotics, and TNFi. Clinical presentation was purpura in 100%, articular in 56%, gastrointestinal in 37%, and renal in 33% of patients [11].

Four immune-mediated syndromes have been attributed to minocycline treatment: serum sickness, DIL, autoimmune hepatitis, and vasculitis [12]. DIL and hepatitis were the most common, manifesting after a protracted use of 2 years. The most frequent symptoms are arthralgia, arthritis, fever, and rash, whereas renal and central nervous system involvement is rare.

Propylthiouracil (PTU) administration has been associated with rare events of DIL and vasculitis. Patients with thyroid disease are more prone to suffer from other autoimmune conditions, making them more susceptible to drug-induced autoimmunity. Aloush et al. [13] described three cases of DIL and one case of vasculitis, which developed in young women after prolonged treatment (>9 months) with PTU. After reviewing the literature, they identified another 30 cases of vasculitis and 12 cases of DIL after PTU treatment. Musculoskeletal symptoms were more prevalent in DIL, whereas renal and pulmonary involvement was more common among PTU-induced vasculitis. Fever, mucocutaneous lesions, serositis, and hematological and gastrointestinal involvement occurred at a lower frequency in both groups.

There have been 22 case reports of asthma patients developing eosinophilic granulomatosis with polyangiitis (EGPA) receiving leukotriene inhibitors [14]. As all the patients were being treated with inhaled or systemic corticosteroids for their asthma, and the onset of CSS was often associated with steroid tapering, it has been suggested that these cases represent unmasking of undiagnosed EGPA with tapering of the steroids rather than a drug-induced disease [15]. Even so, some cases of EGPA may be an idiosyncratic response to leukotriene inhibitors.

Recombinant INF-a treatment has been associated with the emergence of thyroid autoimmunity and dysfunction in different patient groups. Among patients with breast cancer and multiple sclerosis (MS), 30% and 7.7% developed thyroid dysfunction; among patients treated for hepatitis C, 3% and 30% of previously euthyroid patients developed thyroid dysfunction [15]. DIL has been rarely demonstrated (0.15–0.7%).

Following the worldwide introduction of anti-TNF-a in treating rheumatic and Crohn's diseases (CDs), a significant prevalence of autoimmunity has been reported. However, few cases of overt disease have been published. A retrospective national study in France encompassing all the centers prescribing anti-TNF agents for rheumatic diseases and including more than 10,000 patients identified 22 cases of DIL [16]. Whereas 10 patients had only anti-DNA antibodies and skin manifestations, 12 had at least 4 American College of Rheumatology (ACR) criteria for lupus. Selected cases of demyelinating syndromes resembling MS have been described following anti-TNF therapy, albeit only in patients with previous autoimmune disease [rheumatoid arthritis (RA) and CD] and not in patients with spondyloarthropathy (SpA) [17], implying that the effect of anti-TNF may be secondary to an already established autoimmune milieu.

Serological Features

By definition, patients with DIL have antinuclear autoantibodies (ANAs), usually with a homogenous pattern (induced by procainamide, isoniazid, timolol, hydralazine, and phenytoin). In contrast, thiazides have been associated with speckled ANA patterns. Hydralazine and procainamide are related to the induction of several autoantibodies, including ANAs (>95%), anti-histone, usually IgG anti-[H2a-H2B] DNA (>95%), anti-denatured DNA (50%), anticardiolipin (5–15%) antibodies, and rheumatoid factor (RF) (20–30%) [10]. In contrast to SLE, in DIL, the anti-DNA antibody is directed against ssDNA, anti-Sm antibodies are rare, and complement levels are within the normal range.

The most common serological findings in minocycline-induced autoimmunity are ANAs and perinuclear antineutrophilic cytoplasmic antibodies (p-ANCAs). Interestingly, antihistone antibodies are found at a low frequency [12]. In PTU-induced autoimmunity, a 90% prevalence of ANA, 42% prevalence of antihistone, 25% of anti-DNA, and 50% of p-ANCA were found among cases of PTU-induced lupus. In contrast, cytoplasmic ANCA (c-ANCA) was detected only in cases of PTU-induced vasculitis; a similar rate of p-ANCA was found in both conditions, but anti-myeloperoxidase (anti-MPO) antibodies were found at a high frequency in PTU-induced vasculitis [13]. Several cases of drug-induced vasculitis associated with ANCA and anti-MPO specificity have been described after exposure to minocycline, hydralazine, methimazole, and penicillamine [13]. Among patients treated with INF-a, 4–19% developed some form of autoimmunity: 12% developed ANA and 8% dsDNA [19]. However, among hepatitis C patients, a wide range of seroconversion for thyroid autoantibodies has been reported during treatment (up to 40%) and even months after INF-A was terminated [15]. In some patients, the autoantibodies disappeared months after termination of therapy, highlighting the possible direct effect of INF-A on the induction of the antibodies. Similarly, in patients with MS (treated with INF-b) and breast cancer, 19% and 50%, respectively, developed thyroid antibodies [15].

An increase in ANA and anti-dsDNA antibody titers occurs in all groups of patients treated with anti-TNF-a antibodies or fusion proteins [18]. Approximately 67.5% developed ANA after infliximab treatment, and 17.5% developed newly positive anti-dsDNA antibodies [19], albeit only 10 patients developed symptoms of SLE [19]. Interestingly, induction of autoantibodies was higher among patients with SpAs. After 34 weeks of infliximab treatment, newly positive results for ANAs were 32.3% for RA as compared with 71.4% for SpAs, and 11.3% of RA developed anti-DNA antibodies compared with 17.1% among SpA patients (especially non-IgG isotype). In addition, 10–15% of patients in both groups also developed anti-nucleosome and antihistone antibodies. A low prevalence of anti-ENA and anticardiolipin antibodies has also been described in patients treated with anti-TNF-a [16].

Diagnostic Criteria

In the previous edition of this book, we proposed a diagnostic criterion for drug-induced autoimmunity (See Table 11.2). Nevertheless, the attribution of autoimmunity to a drug is complicated by several factors, such as the simultaneous exposure to multiple medications (polypharmacy), the latent period between drug exposure and the appearance of symptoms or signs of disease, and the similarities between a

Table 11.2 Proposed criteria for drug-induced autoimmunity

1. Autoimmunity is absent in the patient before exposure to the drug[a]
2. Autoimmunity develops after the introduction of the offending drug[a]
3. Resolution or improvement of autoimmunity follows discontinuation of the drug (de-challenge)[a]
4. Autoimmunity recurs with repeated drug exposure (re-challenge)[a]

[a] All criteria must be met for the diagnosis of Drug-induced Autoimmunity

drug-induced reaction and an actual illness. Nonetheless, the definition of drug-induced autoimmunity must comply with several temporal criteria to establish that autoimmunity did not exist in the patient before the drug exposure; it developed after the introduction of the offending drug; resolution or improvement of autoimmunity followed discontinuation of the drug; and it recurs with repeated drug exposure. As Xiao and Chang proposed [1], the diagnosis must be taken carefully, where clinical symptoms must be consistent with an autoimmune disease along with previous history and laboratory tests.

Regarding the emergence of autoimmunity, applying the proposed criteria may be difficult. Patients may have subtle signs or be in the process of presenting an autoimmune condition coincident with exposure to a new drug, or they may already harbor autoantibodies without clinical disease before the drug introduction. The development of autoantibodies or the emergence of an autoimmune condition may lag weeks or months after introducing a new drug, making a causal relationship difficult. Finally, the resolution of symptoms and the disappearance of autoantibodies may not follow the discontinuation of the suspected offending drug, as several immune processes may not be readily or rapidly reversed. In addition, by their very nature, autoimmune diseases may present insidiously or atypically, making their diagnosis difficult. In summary, diagnosing a drug-induced autoimmune condition is a process of elimination.

Prognosis

The prognosis of drug-induced autoimmunity is excellent once the causative medication is discontinued. In selected cases, corticosteroids and rarely cytotoxic agents are required. Recovery generally occurs within days or weeks.

Prediction

Traditionally, a distinction has been recognized between the development of autoantibodies following drug exposure and the emergence of an autoimmune disease. The classic case of procaine-induced ANAs has demonstrated that although ANA positivity was detected in many patients, only a tiny minority developed a lupus-like disease. Similarly, and more recently, a high frequency of ANAs has been seen among different groups of patients following treatment with anti-TNF agents [19].

Still, to date, only rare cases have developed overt disease. Predicting who will develop DIL or any other drug-induced autoimmunity is impossible. Predisposing factors for DIL include slow acetylator phenotypes, HLA-DR4, complement C4 null allele, female gender, and Caucasian race [20].

Therapy

For most patients with drug-induced autoimmunity, no specific treatment is required after the offending drug is terminated, although, in selected patients, a short course of corticosteroids is necessary. More aggressive therapy may be needed in rare cases, mainly when vasculitis develops.

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Polyautoimmunity and Multiple Autoimmune Syndromes

12

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Abstract

Autoimmune diseases (ADs) share common mechanisms, risk factors, clinical phenotypes, and treatment. Such commonalities have been called "*autoimmune tautology*". Polyautoimmunity, both overt and latent, indicates the presence of more than one AD or the presence of diverse autoantibodies in a single patient and is considered the clue for the understanding of the variability, but also similarity, among ADs. Herein, we describe the evidence of PolyA as the basis for autoimmune tautology and the implications for the development of a new taxonomy of ADs.

Keywords

Autoimmune tautology · Polyautoimmunity · Latent autoimmunity · Overt autoimmunity

Abbreviations

ACPA	Anti-citrullinated protein antibodies
ADs	Autoimmune diseases
AITD	Autoimmune thyroid disease
APS	Antiphospholipid syndrome
ds-DNA	Anti-double-stranded DNA
PolyA	Polyautoimmunity
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SLE	Systemic lupus erythematosus
SS	Sjögren's syndrome
SSc	Systemic sclerosis
T1DM	Type 1 diabetes mellitus
Tg	Thyroglobulin
TPO	Thyroperoxidase

Description of the Disease

Autoimmune diseases (ADs) are a chronic and clinically heterogeneous group of diseases affecting around 5% of the world population [1], and recent studies have suggested an increase in their incidence. These conditions share risk factors and immunological mechanisms, which illustrates that one AD coexists with others and that one AD shows positivity for autoantibodies with diverse specificity (Table 12.1).

Such coexistence advocates that one condition may evolve from one to another AD simultaneously, or in the opposite direction, that ADs belong to the same spectrum of a single condition with multiple clinical manifestations and immunological phenotypes. Thus, suggesting that current classification criteria and labels of "Primary" or "Secondary" ADs are inaccurate. In this line, a molecular classification of autoimmunity may allow a better diagnosis and management of these conditions.

Modifying the paradigm for ADs' classification requires that the molecular and immunological basis of autoimmunity are translated into clinical phenotypes with specific immuno-

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Table 12.1 Serological markers in polyautoimmune disease

IgG autoantibodies	RA (%)	SLE (%)	SS (%)	SSc (%)	AITD (%)
U1-snRNP B/B′	41.8	77.8	89.7	88.2	47.1
Thyroglobulin	29.5	31.1	51.7	41.2	88.2
ssRNA	8.2	82.2	10.3	17.6	29.4
SM	22.6	88.9	51.7	41.2	29.4
Ro/SSA	17.6	42.2	62.1	52.9	17.6
Ribo phosphoprotein P1	11.8	53.3	37.9	52.9	11.8
Laminin	29.4	42.2	55.2	29.4	29.4
Histone H2A	35.3	68.9	27.6	23.5	35.3
dsDNA	23.5	82.2	13.8	11.8	23.5
CENP-A	17.6	22.2	6.9	82.4	17.6

U1-snRNP B/B′: U1 small nuclear ribonucleoprotein particle (snRNP) B/B′ complex; ssRNA: single-stranded RNA; SM: Smith ribonucleoprotein; Ro/SSA; dsDNA: double-stranded DNA; CENP-A: centromere protein A
Taken and updated from [2]

modulatory management. However, diagnosis of autoimmunity based on this new paradigm could be challenging. Novel strategies including the measurement of autoantibodies with diverse specificities, and new statistical models would help to develop this new taxonomy as well as prevention and therapy strategies for this specific population. In addition, it is unknown whether combinations of latent and overt autoimmunity (i.e., clusters) may have implications for long-term outcomes.

Herein, we describe the concept of polyautoimmunity (PolyA) and its utility in the validation of autoimmune tautology. In addition, we provide further discussion for the development of a new taxonomy of ADs based on molecular and immunological signatures which may influence the management of these conditions.

What Is Polyautoimmunity?

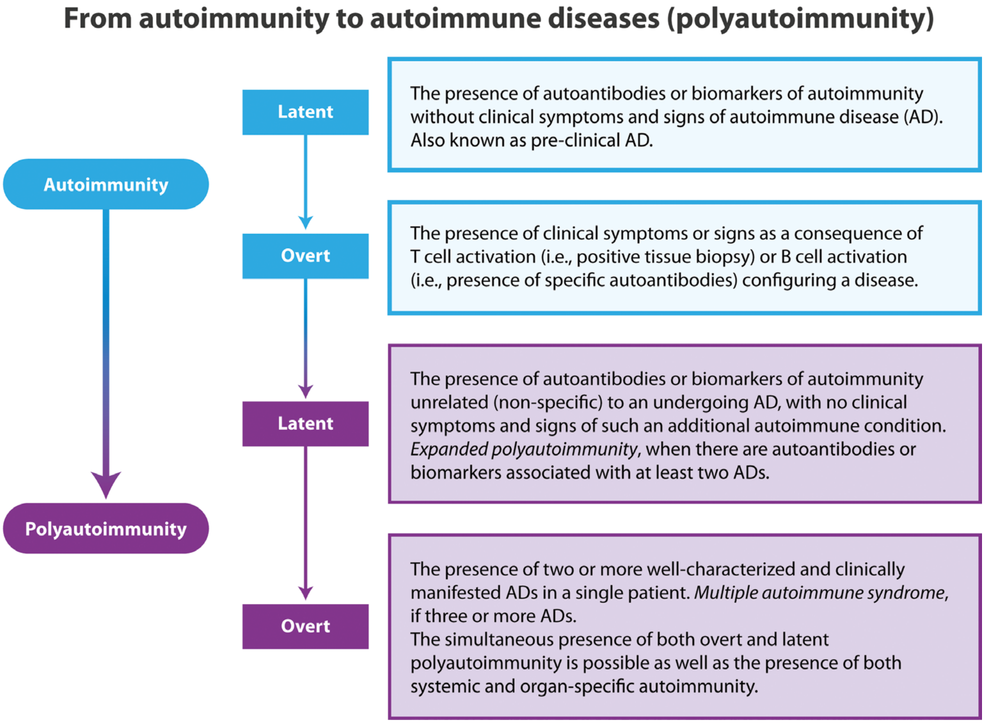
ADs may be presented as a single entity or as a combination of them. The latter condition is known as PolyA (i.e., two or more ADs in a single patient) [1]. PolyA was introduced to the medical terminology in 1993. There were two manuscripts describing patients with more than one AD. The first one was in March 1993 by Sheehan et al. [3] illustrating a young woman presenting with rheumatoid arthritis (RA), idiopathic thrombocytopenic purpura, pernicious anemia, Hashimoto's thyroiditis, systemic sclerosis (SSc), pancreatic exocrine insufficiency, and coeliac disease.

The second one was in November 1993, published by Tanus et al. [4] in which a patient with variable immunodeficiency presented with vitiligo, atrophic gastritis, pernicious anemia, and primary biliary cholangitis was described. Then, 15 years later, we published a paper describing PolyA and familial autoimmunity in SSc [5]. Since then, the interest of the scientific community has been increasing. Today there are more than 200 papers about PolyA in the literature, including multiple autoimmune syndrome (MAS), which corresponds to the presence of three or more well-established ADs.

More recently, a deeper characterization of PolyA was pursued. The coexistence of two or more ADs fulfilling classification criteria was termed "*Overt PolyA*", whereas the presence of autoantibodies unrelated to the index AD, without criteria fulfillment, is named "*Latent PolyA*" (Fig. 12.1). In addition, both conditions can coexist in a single patient. Latent PolyA is based on recent evidence that the positivity of autoantibodies predates the appearance of overt PolyA, and suggests that despite the index condition, patients with autoimmunity present autoantibodies with diverse specificities. This new terminology should help to avoid the use of "*overlap syndromes*" since it omits several other systemic and organ-specific ADs that are also associated with each other and observed among them, including latent and overt PolyA.

Several risk factors have been linked to the development of PolyA in different ADs. In patients with RA, coffee consumption, coffee plus tobacco consumption, and coffee intake plus hair dye use were associated with the development of PolyA (i.e., autoimmune ecology) [7]. Rhupus has been defined as a disease in which characteristics of both RA and systemic lupus erythematosus (SLE) are present in the same patient. Furthermore, in patients with RA and SLE, older age, and late age at onset were associated with the development of Rhupus (Table 12.2).

First-degree relatives of patients with SLE were more likely to present latent PolyA for RA, autoimmune thyroid disease (AITD), type 1 diabetes mellitus (T1DM), and antiphospholipid syndrome (APS). Factors such as age and gender were associated with the development of this type of PolyA. In another study, gender, articular compromise, familial autoimmunity, and ancestry (Colombia vs. Spain) were associated with PolyA in SLE [9]. In addition, having SLE and Sjögren's syndrome (SS) plus tobacco consumption was associated with the development of AITD [10] (Table 12.2).



The presence of autoantibodies or biomarkers of autoimmunity without clinical symptoms and signs of autoimmune disease (AD). Also known as pre-clinical AD.

The presence of clinical symptoms or signs as a consequence of T cell activation (i.e., positive tissue biopsy) or B cell activation (i.e., presence of specific autoantibodies) configuring a disease.

The presence of autoantibodies or biomarkers of autoimmunity unrelated (non-specific) to an undergoing AD, with no clinical symptoms and signs of such an additional autoimmune condition. *Expanded polyautoimmunity*, when there are autoantibodies or biomarkers associated with at least two ADs.

The presence of two or more well-characterized and clinically manifested ADs in a single patient. *Multiple autoimmune syndrome*, if three or more ADs.
The simultaneous presence of both overt and latent polyautoimmunity is possible as well as the presence of both systemic and organ-specific autoimmunity.

Fig. 12.1 Continuum spectrum of polyautoimmunity. From latent to overt autoimmune diseases. *AD* autoimmune disease. (Taken and adapted from [6])

Table 12.2 Factors associated with overt polyautoimmunity in autoimmune diseases

Disease	Type of polyautoimmunity	Associated factors
Systemic lupus erythematosus	Overt PolyA	Older age and age at onset [8] Gender, articular compromise, familial autoimmunity and ancestry (Colombia vs. Spain) [9] Tobacco consumption for the development of AITD [10]
	Latent PolyA	Familial autoimmunity, age, and sex [11]
Rheumatoid arthritis	Overt PolyA	Coffee, tobacco, and hair dyes [7]
Type 1 diabetes mellitus	Overt PolyA	Ancestry (Caucasians), age, and sex [12]

PolyA: polyautoimmunity; AITD: autoimmune thyroid disease

In patients with T1DM, Caucasians were more likely than other ethnicities to have an additional autoimmune disease, and the prevalence of autoimmunity increased with age, significantly in women. This, suggests that most patients may require time to develop a second AD, and the development of synchronous overt PolyA is less common.

In the study of Alarcón-Segovia and colleagues [13], it was found that there is a familial aggregation of SLE, RA, and other ADs. Amerindian ancestry and higher socioeconomic status were associated with familial autoimmunity in SLE. This study confirms that familial autoimmunity is one of the most critical factors for the diversity of ADs, and their cooccurrence in patients with PolyA.

As previously revised [14], *PolyA* "*may represent the effect of a single genotype and similar environmental factors on diverse phenotypes, and it is associated with female gender, familial autoimmunity, Amerindian ancestry, and cigarette smoking*". All the above-mentioned data indicate that PolyA is a complex trait in which multiple etiological factors converge, and confirms that autoimmunity is a single trait with multiple clinical and immunological manifestations, that is, it is a syndrome rather than a single condition.

Immunological and Genetical Basis of Polyautoimmunity

Studies focused on PolyA have found that polymorphisms *HLA-DRB1, HLA-DQB1, CD226, PTPN22, STAT4, GPR103, TNFAIP3,* and *LRP1/STAT6* are associated with its development. Interestingly, genetic studies have shown that most polymorphisms associated with ADs are shared among all of them. In addition, a meta-analysis on AITD showed that some populations had higher frequencies of latent or overt PolyA (i.e., Asia and Europe) than other latitudes [15]. This evidence supports the link between genetic predisposition and ancestry in the development of PolyA.

Recent studies in SLE showed that autoantibody-based classification allowed the identification of subgroups associated with disease activity, and inflammatory cytokines [16].

In addition, another study showed the association between IL-12/23p40 and overt PolyA [17], suggesting a differential expression of cytokines, that can be used as therapeutic targets in patients with PolyA.

A study on megakaryocyte expansion in peripheral blood showed that patients with SS, SLE, and RA shared similar transcriptional profiles and common gene expression signatures associated with nucleosome assembly and hemostasis. This confirmed that ADs shared a common pathophysiology and explained the coexistence of latent and overt PolyA. In another study, a cluster analysis yielded that ADs exhibit differential immunological profiles based on PolyA, thus suggesting that despite similarities among ADs, PolyA is a critical factor for the classification and treatment of these conditions.

Those clusters gathering most of the overt and latent PolyA showed dysregulation of multiple inflammatory and anti-inflammatory cytokines such as IL-12p70 and IL-17A [2]. Furthermore, cytokine production is pivotal in the pathophysiology of ADs and may influence the synthesis of autoantibodies.

In SLE, the role of IL-1β, IL-6, and IL-8 in nephritis has been confirmed [18]. Elevated levels of IL-12 and IL-23 have been associated with anti-double-stranded DNA (ds-DNA) antibodies [19]. The serum IL-12p40 was elevated in patients with SLE and correlated with the activity of the disease [20]. In the case of SSc, IL-6 and IL-13 are associated with skin fibrosis [21], whereas IL-5 and IL-17 are implicated in interstitial lung disease [22]. However, reduced levels of IL-10 after in vitro stimulation are characteristic of SSc [23]. In RA, high IL-6 levels have been associated with bone erosions and anti-citrullinated protein antibodies (ACPA) positivity, while in SS, IL-17 has been associated with disease severity [24].

All the above data confirms the pleiotropic effects of genes, autoantibodies, and cytokines in the pathophysiology of ADs, but at the same time, confirms that all ADs are based on an identical immunological profile with distinctive clinical manifestations. This supports that ADs are a single trait rather than many.

Prevalence of Latent and Overt Polyautoimmunity

Overall, latent PolyA is present in about 70% of all patients with ADs, and AITD (82.4%) and SLE (40%) yield the highest frequency of overt PolyA [2]. Prevalence of overt PolyA is about 33–52% in SS [25], 14% in RA [7], 33% in coeliac disease [26], 32% in primary biliary cholangitis [27], 27% in vitiligo [28], 13% in Myasthenia Gravis [29], 8–26% in multiple sclerosis [30], 26–38% in SSc [5], and up to 20.1% in T1DM [12].

Regarding latent PolyA, in SLE, rheumatoid factor (RF) and ACPA are present in 42% and 6%, respectively, but only 6.4% of patients meet the criteria for Rhupus [8]. Antiphospholipid antibodies may be present in 54% of SLE patients; however, APS develops in about 10% of those patients [8]. In euthyroid patients with SLE, thyroperoxidase (TPO) and thyroglobulin (Tg) autoantibodies are observed in 21% and 10% of patients, respectively. However, confirmed autoimmune hypothyroidism is observed in only 12% of SLE patients [8].

In RA, the frequency of AITD is 10%, whereas the presence of TPO and Tg is 38% and 21%, respectively [31]. In SS, AITD is observed in 15–30% of patients, RA in 4–31%, SLE in 9–19%, and SSc in 14% [32]. In SSc, AITD and SS are observed in 23% and 15% of patients respectively [5]. This confirms that latent PolyA is common and predictive of overt PolyA. In addition, all the above data advocates that overt and latent PolyA should be routinary evaluated in any patient with ADs, epidemiological studies, and clinical trials.

Polyautoimmunity has also been studied in the pediatric population. Malagon et al. [33] evaluated 313 children with overt PolyA. PolyA occurred simultaneously in 138 (44%) patients. Multiple autoimmune syndrome was observed in 62 (19.8%) patients. There were 25 index diseases of which, systemic lupus erythematosus (SLE, $n = 134$, 42.8%), juvenile idiopathic arthritis (JIA, $n = 40$, 12.7%), Hashimoto's thyroiditis (HT, $n = 24$, 7.66%), immune thrombocytopenic purpura (ITP, $n = 20$, 6.39%), antiphospholipid syndrome (APS, $n = 15$, 4.79%), and vitiligo (VIT, $n = 15$, 4.79%) were the most frequent and represented 79.23% of the total number of patients. Familial autoimmunity influenced PolyA. A high aggregation of autoimmunity was observed ($\lambda r = 3.5$). Three main clusters were identified, of which SLE and APS were the most similar pair of diseases (based on the Jaccard index) followed by HT and JIA, which were related to ITP and Sjögren's syndrome. The third cluster was composed of localized scleroderma and VIT.

Multiple Autoimmune Syndrome

Multiple autoimmune syndrome (MAS) is defined as the presence of three or more distinct ADs in one patient. They can be further divided into three main groups according to Humbert and Dupond: MAS-1 (includes myasthenia gravis, thymoma, polymyositis, and giant cell myocarditis); MAS-2 (includes SS, RA, primary biliary cholangitis, SSc, and autoimmune thyroid disease); and MAS-3 (groups together autoimmune thyroid disease, myasthenia gravis and/or thymoma, SS, pernicious anemia, idiopathic thrombocytopenic purpura, Addison's disease, type 1 diabetes mellitus, vitiligo, autoimmune hemolytic anemia, SLE, and dermatitis herpetiformis) [34]. However, this classification is outdated and other studies during the last decades have suggested other ADs not previously reported in the Humbort and Dupond classification.

Other syndromes such as autoimmune polyglandular syndromes (APS) were also recognized and classified by Neufeld and Blizzard into four groups: APS-1 (encounters chronic mucocutaneous candidiasis, chronic hypoparathyroidism, and Addison's disease); APS-2 (Addison's disease with AITD and/or type 1 diabetes mellitus); and APS-4 (includes any combination of ADs that does not fall into other categories). As noticed, APS-3 was later updated into APS-3A (AITD with type 1 diabetes mellitus), APS-3B (AITD with atrophic gastritis and/or pernicious anemia), and APS-3C (AITD with alopecia, vitiligo, myasthenia gravis, or any other ADs) [35]. Nevertheless, the term APS has also evolved over the years because ADs were not simplified only to polyglandular disease, but instead, other non-endocrine ADs should be included as well. As a result, some authors argue that APS as well as MAS correlate to different forms of PolyA and therefore, a common genotype is shared.

Clinical Significance of Polyautoimmunity

Despite the high frequency of PolyA, little is known about its clinical influence on outcomes. It seems that depending on the index condition and the type of PolyA, the severity of the disease fluctuates. Patients with Rhupus exhibit a more erosive disease and it is associated with ACPA antibodies, higher incidence of malignancy in RA-SS, low rates of remission in Myasthenia Gravis-AITD, a more severe disease in T1DM-celiac disease, in SLE-APS, and SLE-Vasculitis. On the other hand, other reports suggest that overt PolyA may influence better outcomes. In contrast, the course of the combination of Myasthenia Gravis-AITD and SSc-AITD appears to be milder.

Since PolyA is a complex trait, cluster analysis has yielded insights into the influence of PolyA in outcomes. In the study of Rojas et al. [2], cluster analysis showed that latent and overt PolyA cluster together. In addition, those subgroups gathering most of the PolyA exhibited a pro-inflammatory phenotype and required a greater number of treatments simultaneously. In a similar study on SLE, clustering of autoantibodies showed that this condition presents with differential clinical manifestations, as well as association with specific *HLA* alleles.

Paving the Way for the Autoimmune Tautology

As discussed above, ADs share several clinical signs and symptoms (i.e., phenotypes) as shown in Table 12.3, immunological mechanisms, and genetic factors. Such commonalities among ADs have been called autoimmune tautology [36]. As previously revised: "*Tautology (from Greek tauto, "thesame" and logos, "word/idea") is an obvious statement. In logic theory, tautology is a statement that is always true in every possible interpretation. Thus, autoimmune tautology means that one AD is similar to a second one, to a third one, and so on. ADs are comparable but not equal given the fact the cell and organ targets are different in each case*".

Table 12.3 Most common signs and symptoms in polyautoimmunity

Sign/symptom	Percentage (%)
Arthralgias	90.2
Arthritis	74.3
Xeropthalmia	50.3
Xerostomia	45.4
Menstrual disorders	26.6
Myalgia	18.6
Miscarriage	18.5
Gastritis	16.4
Anemia	13.1
Photophobia	12.6
Raynaud	12.6
Alopecia	11.5
Telangiectasias	7.7
Dysphagia	7.1
Preeclampsia	6.4
Preterm delivery	5.7
Sclerodactyly	5.5
Oral ulcers	4.4
Goiter	3.8
Skin nodules	3.3
Vascular thrombosis	3.3
Microstomia	3.2
Malar rash	2.7
Weight loss	2.2
Infertility	1.1
Periorbital edema	1.1
Seizures	1.1
Urticaria	1.6
Episcleritis	0.6
Pulmonary nodules	0.5
Calcinosis	0.5

Taken and updated from [2]

The main premises of autoimmune tautology include: (1) Preponderance of females, (2) Similar pathophysiology, (3) Similar clinical presentation, (4) The severity of the disease is inversely related to the age of onset, (5) Similar environmental agent, (6) Ancestry might influence the clinical presentation, (7) Common genetic factors, (8) PolyA, (9) Familial autoimmunity, and (10) Similar pharmacological treatment.

PolyA could be considered the foundation of autoimmune tautology. As described above, most of the patients exhibit latent or overt PolyA; clinical manifestations are shared across ADs due to PolyA; PolyA clusters showed common genetic and immunological pathways with unique clinical manifestations and pharmacological treatments; patients with PolyA exhibit similar environmental risk factors, and ancestry may influence the onset of some types of PolyA.

Table 12.4 Common laboratory findings in polyautoimmunity

Laboratory finding
Clinical inflammatory markers
Elevated erythrocyte sedimentation rate (ESR)
Elevated C-reactive protein (CRP)
Fibrinogen
Complete blood count markers
Leukopenia[a]
Lymphopenia[a]
Hemoglobin[a]
Others
Thyroid stimulating hormone (TSH)
Proteinuria
High creatinine levels
Low complement levels (C3 and/or C4)

Laboratory findings can exhibit significant variability based on the specific autoimmune diseases affecting the patient. As a result, these laboratory findings should be carefully individualized. (Taken and updated from [2])

[a] Commonly manifesting with lower levels

Diagnostic Criteria

PolyA remains a heterogeneous disease, and a definitive diagnostic criterion has not been established. As previously described, PolyA comprises multiple clinical signs and symptoms depending on the ADs present in the patient, and therefore, the disease course differs from patient to patient. In addition, PolyA subphenotypes may fluctuate depending on the duration and activity of the disease as well as laboratory markers (Table 12.4).

However, we propose the following criteria for Overt PolyA: (1) two or more well-characterized and clinically manifested ADs in a single patient; (2) the presence of clinical signs and/or symptoms related to Ads; and (3) the presence of autoantibodies or biomarkers of autoimmunity. For MAS, we would only consider three or more ADs.

In the case of latent PolyA: (1) positivity for autoantibodies not related to overt autoimmunity, or in the absence of any well-defined clinical condition; (2) the lack of clinical signs and/or symptoms related to ADs associated with such autoantibodies; and (3) the presence of other autoantibodies or biomarkers of autoimmunity associated with the autoimmune condition related to latencies.

Can the Disease Be Predicted, and Give PPV and NPV?

It is well known that autoimmunity could be predicted based on risk factors and the presence of latent autoimmunity. However, how such factors are involved in the prediction of PolyA is still unclear. Multiple combinations of phenotypes could emerge in a single patient, and this may rely on genetics, and environmental factors, which make it harder. In this line, it is of critical importance to implement multivariate models integrating proteomics, metabolomics, and transcriptomics, to uncover the intricated pathways that lead to the development of PolyA, and develop predictive signatures for the prevention and management of the disease.

Therapy and Prevention

There is no specific therapy for PolyA. However, a recent study showed that management with hydroxychloroquine in SLE could be associated with a lower frequency of PolyA, as well as a delay in its development. This suggests that treatment at the early stages of the disease with DMARDs could have a positive impact on preventing it. However, further longitudinal studies, as well as the evaluation of other index conditions, are required. Treatment of the index disease should be offered according to clinical guidelines.

Conclusion

PolyA is a frequent condition, and it is a major premise sustaining the autoimmune tautology hypothesis. The assessment and clustering of PolyA will help to define plausible approaches to studying the common mechanisms of these diseases (i.e., the autoimmune tautology). Identification of commonalities among ADs may provide insights about salient mechanisms that are necessary, and perhaps sufficient for autoimmunity to occur. In addition, PolyA, as an extreme phenotype of autoimmunity, would be critical for dissecting genes of major effect conferring susceptibility to autoimmunity.

Declaration of Competing Interest None.

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Part II

Systemic Vasculitis

Giant Cell Arteritis

13

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Abstract

Giant cell arteritis (GCA) is the most common form of systemic vasculitis in adults. It predominantly affects the aorta and its major branches, including the temporal arteries. It mainly affects individuals over 50 years of age, with a higher incidence in whites and women. The worldwide pooled annual incidence is 10 per 100,000, with variations between populations: highest incidence in Scandinavians and Americans, lowest in Africans and East Asians. The estimated prevalence is 51.74 per 100,000 in people over 50 years of age. GCA is thought to be triggered by T cells responding to an unknown antigen. This leads to immune cell infiltration of affected arteries and cytokine production with local and systemic effects. Symptoms can be divided into four subsets: cranial arteritis, extracranial arteritis, systemic symptoms, and polymyalgia rheumatica. Common symptoms include new-onset temporal headache and jaw claudication. Serious complications can include blindness and cerebrovascular accidents. High erythrocyte sedimentation rate, elevated C-reactive protein, inflammatory anemia and thrombocytosis are common biomarkers associated with GCA. There are no specific diagnostic criteria for GCA. The American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) published updated classification criteria in 2022. These criteria are for research and not for clinical diagnosis. The criteria aim to standardize research cohorts, but are not suitable for clinical diagnosis. Diagnosis should be considered based on the basis of clinical manifestations and laboratory findings. No single feature has a high predictive value for GCA. The pretest probability should guide further investigations. Temporal artery biopsy (TAB) has historically been considered the gold standard for cranial GCA. Sensitivity varies due to factors such as sampling quality and extracranial vasculitis. Imaging techniques such as ultrasound (US), magnetic resonance imaging (MRI), and fluorodeoxyglucose-positron emission tomography (FDG-PET) have become relevant for diagnosis. US is cost-effective and non-invasive, but operator-dependent. MRI and FDG-PET may be alternatives in certain cases. GCA is a medical emergency and treatment should not be delayed. Glucocorticoids are the mainstay of treatment. Tocilizumab or methotrexate can be used in combination with glucocorticoids. Aspirin may be considered to prevent ischemic events.

Keywords

Giant cell arteritis · Systemic vasculitis · Aorta · Temporal arteries · Headache · Jaw claudication · Biomarkers · Diagnostic criteria · Classification criteria · Temporal artery biopsy · Ultrasound · Glucocorticoids · Tocilizumab · Methotrexate · Aspirin

Introduction

Giant cell arteritis (GCA) is the most common form of systemic vasculitis in adults. GCA is a granulomatous arteritis usually affecting the aorta and/or its main branches, with a predilection for the branches of the carotid and vertebral arteries [1].

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Epidemiology

GCA predominantly affects Caucasian individuals over the age of 50: the disease almost never occurs in younger individuals and its incidence increases with age. Women are more affected than men by a ratio of 2.5:1. The worldwide pooled annual incidence of GCA is 10 per 100,000 but varies widely in different populations: the highest incidence is found in Scandinavians (21.57/100,000) and Americans (10.89/100,000), an average incidence is estimated in Oceania (7.85/100,000) and Europe (7.26/100,000), while the lowest incidence is reported in Africans (4.62/100,000) and in East Asians (0.34/100,000). The estimated prevalence is 51.74 per 100,000 persons aged 50 years and over [2].

Pathogenesis

The pathogenesis of GCA appears to be initiated by T cells responding to an unknown antigen, leading to immune cell infiltration of the affected artery and the production of cytokines that cause local damage and systemic effects [3].

Clinical Manifestations

The signs and symptoms of GCA can be divided into four subsets: manifestations of cranial arteritis, extracranial arteritis, systemic symptoms, and polymyalgia rheumatica (PMR) (Table 13.1). The most common symptom is the new-onset temporal headache, while jaw claudication is the most specific. On physical examination, the temporal arteries may be tender or thickened, and pulses may be diminished. Severe cranial ischemic events associated with GCA include blindness and cerebrovascular accidents. Extracranial involvement in GCA involving the aorta and its major branches [large vessel vasculitis GCA (LV-GCA)] may be asymptomatic or present with limb claudication, vascular bruits, and diminished or absent pulses. Late potential complications include valvular heart disease and aortic aneurysms and/or dissections [4, 5]. PMR is closely associated with GCA: 40–60% of patients with GCA have PMR, while 15–20% of those with PMR develop GCA symptoms [4].

Table 13.1 Frequency and symptoms associated with giant cell arteritis [4, 5]

Clinical feature	Frequency (%)
Constitutional symptoms	
Fever, malaise, fatigue, anorexia, weight loss	30–60
Cranial arteritis	
Headache	65–90
Abnormal temporal artery on examination (prominent or tender)	30–60
Jaw or tongue claudication	30–50
Scalp tenderness	30–50
Acute visual defects (sudden vision loss, diplopia)	30–40
Tongue or scalp infarction	<5
Otolaryngologic manifestations such as hearing loss, tinnitus, vertigo, dizziness, or abnormal vestibular testing	5–25
Neurological symptoms like stroke, transient ischemic attack, confusion	3–10
Extracranial arteritis	
Respiratory symptoms such as dry cough, sore throat, or choking sensation	5–20
Aortic arch syndrome, aortic-valve insufficiency, aortic aneurysm and dissection, limb claudication, vascular bruits	<15
Peripheral neuropathies, myelopathy, or mononeuritis	<15
Polymyalgia rheumatica	
Bilateral aching and stiffness of the shoulder girdle, sometimes the neck and hip girdle	30–60

Table 13.2 Performance of laboratory findings and biomarkers in GCA [6]

TEST	Sensitivity (%)	Specificity (%)
Acute phase reactants		
Erythrocyte sedimentation rate	65.5–91.5	29.5–57.3
C-reactive protein	66.9–96.2	41.3–67.9
Full blood count		
Thrombocytosis	51.9–80	62.6–79.3
Anemia	61.7	52.2

Several studies have evaluated various laboratory biomarkers associated with GCA and its activity. High erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP), anemia of inflammation, and thrombocytosis are the most used biomarkers in routine care (Table 13.2) [6].

Table 13.3 provides a thorough summary of the main features and other factors to consider in the differential diagnosis of GCA.

Table 13.3 Differential diagnosis of giant cell arteritis

Diagnosis	Key features	Additional considerations
Polymyalgia rheumatica	• Commonly coexists with GCA • Elevated ESR and/or CRP	• Symptoms: muscle pain, stiffness in shoulder and hip girdle • Responsive to low-dose corticosteroids
Rheumatoid arthritis	• Joint pain and stiffness • Radiographic evidence of joint erosion	• Positive RF and/or anti-CCP antibodies
Systemic lupus erythematosus	• Systemic symptoms (fatigue, joint pain, rashes)	• Positive ANA and/or anti-dsDNA antibodies
Vasculitis	• Other forms (Takayasu arteritis, polyarteritis nodosa) • Elevated ESR and/or CRP	• Symptoms: systemic symptoms, signs of vascular inflammation • Angiographic evidence of vascular involvement
Infection	• Endocarditis, meningitis • Positive blood cultures and/or CBC analysis	• Symptoms: fever, malaise, signs of systemic infection
Malignancy	• Lymphoma, leukemia • Abnormal CBC and/or imaging findings	• Symptoms: weight loss, night sweats, lymphadenopathy
Stroke	• Sudden onset of neurological deficits	• Imaging evidence of cerebral infarction or hemorrhage
Temporal lobe epilepsy	• Recurrent, unprovoked seizures	• Abnormal EEG findings
Temporomandibular joint disorder	• Pain in jaw joint and in the muscles that control jaw movement	• Symptoms: difficulty chewing, change in the way the upper and lower teeth fit together, grating sensation when using the jaw
Non-arteritic anterior ischemic optic neuropathy	• Sudden vision loss in one eye	• Cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia, smoking)

Anti-CCP anti-cyclic citrullinated peptide antibodies, *Anti-dsDNA* anti-double stranded DNA (anti-dsDNA) antibodies, *ANA* antinuclear antibodies, *CBC* complete blood count, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *RF* rheumatoid factor

Diagnostic Criteria

There are no established diagnostic criteria for GCA. Classification criteria were first developed by the American College of Rheumatology (ACR) in 1990. Since then, new clinical manifestations of the disease have been described and the widespread use of advanced vascular imaging techniques has changed the diagnostic approach of the disease. For these reasons, the ACR and the European Alliance of Associations for Rheumatology (EULAR) published new updated classification criteria in 2022 (Table 13.4). These criteria are designed to differentiate GCA from other forms of vasculitis and to allow clinical trials to have uniform cohorts in research setting and therefore not suitable for diagnosis [7]. The diagnosis of GCA should be considered in a patient with suspicious clinical manifestations and laboratory findings and further investigations should be selected based on pre-test probability. A recent meta-analysis showed which features, when present, should increase or decrease the likelihood of suspecting GCA (likelihood ratio: LR). Limb claudication (LR 6.01), jaw claudication (LR 4.9), temporal artery abnormalities (LR 2.29), platelet count of greater than 400 × 10^3/μL (LR 3.75), ESR greater than 100 mm/h (LR 3.11), and anterior ischemic optic neuropathy (LR 2.15) appeared to be more predictive of GCA, while age 70 years or younger (LR 0.48), CRP less than 2.5 mg/dL (LR 0.38), and ESR of no greater than 60 mm/h (LR 0.42) decreased the likelihood of GCA. Although current or previous diagnosis of PMR did not reach statistical significance as a positive predicting feature, the diagnosis of GCA should be excluded in all patients with PMR because of the close association between the two diseases. However, no single feature is likely to shift the pre-test probability sufficiently to make further investigation for GCA unnecessary [4].

Table 13.4 2022 ACR and EULAR classification criteria for GCA [7]

CONSIDERATIONS WHEN APPLYING THESE CRITERIA • These Classification Criteria should be applied to classify the patient as having giant cell arteritis when a diagnosis of medium-vessel or large-vessel vasculitis has been made • Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria	
ABSOLUTE REQUIREMENT	
Age $\geq$50 years at the time of diagnosis	
ADDITIONAL CLINICAL CRITERIA	
Morning stiffness in shoulders/neck	+2
Sudden visual loss	+3
Jaw or tongue claudication	+2
New temporal headache	+2
Scalp tenderness	+2
Abnormal examination of the temporal artery	+2
LABORATORY, IMAGING, AND BIOPSY CRITERIA	
Maximum ESR $\geq$50 mm/h or maximum CRP $\geq$10 mg/L	+3
Positive temporal artery biopsy or halo sign on temporal artery ultrasound	+5
Bilateral axillary involvement	+2
FDG-PET activity throughout aorta	+2
Sum the scores for 10 items, if present. A score $\geq$6 points is needed for the classification for GIANT CELL ARTERITIS	

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *FDG-PET* fluorodeoxyglucose positron emission tomography

Temporal artery biopsy (TAB) is still considered the gold standard procedure and is recommended by the ACR as the initial diagnostic approach for cranial GCA [8]. The classic histological picture is a segmental transmural granulomatous inflammatory infiltrate associated with marked disruption of the internal elastic membrane and the presence of giant cells [9] (Fig. 13.1). TAB has the advantage of having a high specificity (~100%) and of allowing a correct differential diagnosis between GCA and other diseases (ANCA-associated vasculitis, polyarteritis nodosa, cryoglobulinemic vasculitis, amyloidosis, etc.). Conversely, the sensitivity varies widely in different studies (39–77.3%), mainly due to poor sampling, limited accessibility to the procedure, segmented nature of the pathological findings (skip lesions), and the presence extracranial vasculitis, which has less temporal arterial involvement [10]. A long-segment biopsy sample (>1 cm) within 2 weeks of starting treatment is recommended to increase its sensitivity [8].

Over the last decade, imaging has become increasingly important in the diagnosis of GCA, especially in centers where timely TAB is difficult to perform. Many studies have investigated the diagnostic accuracy of temporal artery ultrasound (US) in GCA. The most characteristic US findings are the *halo sign* (a homogeneous hypoechoic thickening of the arterial wall) (Fig. 13.2) and the *compression sign* (the thickened arterial wall remains visible on compression) [11]. A recent meta-analysis described a pooled sensitivity of 84% and a specificity of 95% for these two signs when evaluated together compared with the clinical diagnosis of GCA [12]. US has the advantage of being a cost-effective, non-invasive, and rapid procedure, allowing other vascular territories to be examined, such as the axillary and carotid arteries, thus increasing the diagnostic yield of the test. Conversely, it has the limitation of being an operator-dependent procedure. In addition, its ability to detect signs of inflammation is significantly reduced in cases where arterial involvement is limited to the adventitial layer or to small-caliber collateral vessels [13]. In light of these data, EULAR recommends US of the temporal and axillary arteries as the first imaging modality in patients with suspected cranial GCA and states that in patients with high clinical suspicion and a positive imaging test, the diagnosis of GCA may be made without additional testing (biopsy or imaging) [14].

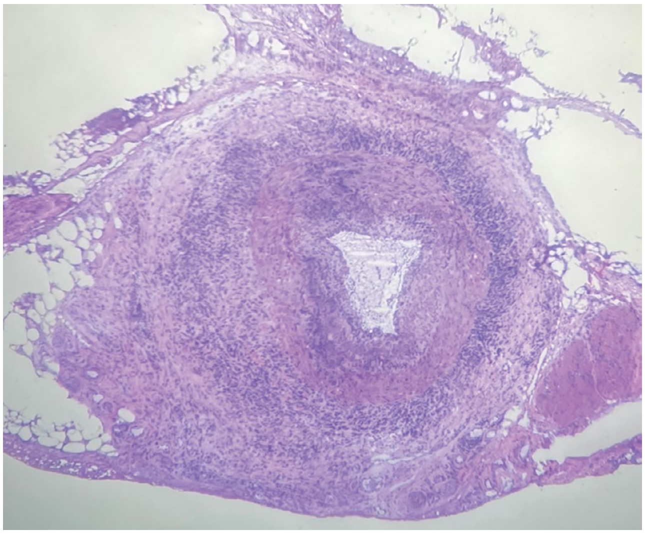


Fig. 13.1 Representative histopathological image of temporal artery biopsy in giant cell arteritis (GCA). The image shows a hematoxylin and eosin-stained section of a temporal artery biopsy taken from a patient suspected of having GCA. The pathological examination reveals transmural inflammation with dense infiltration of lymphocytes and mononuclear cells affecting all layers of the arterial wall. Additionally, the internal elastic lamina shows focal disruption, further supporting the diagnosis. Magnification: 400×

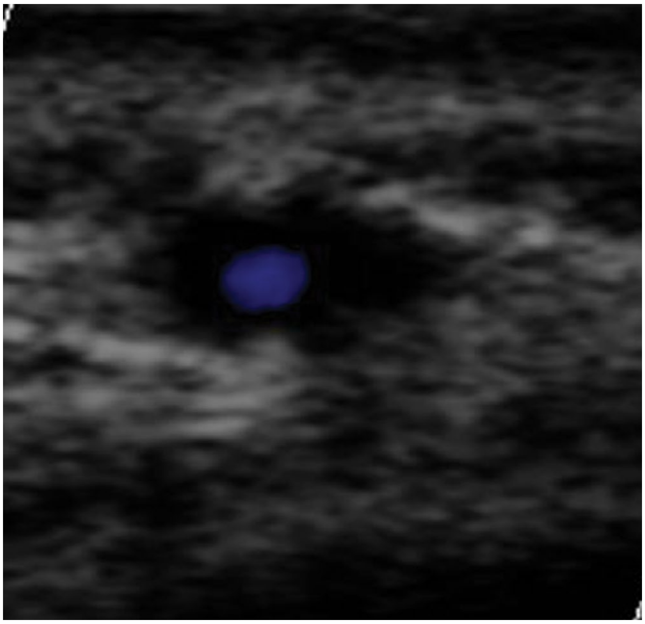


Fig. 13.2 Pathological temporal artery ultrasound revealing abnormal wall thickening and hypoechoic halo in suspected giant cell arteritis (GCA). The image shows an ultrasound of a temporal artery from a patient suspected to have GCA. The examination reveals abnormal wall thickening and a hypoechoic halo around the vessel, indicating inflammation and consistent with GCA

Magnetic resonance imaging (MRI) of the scalp arteries may be used as an alternative diagnostic modality for cranial GCA, especially when US is not available or the results are inconclusive [14]. A meta-analysis comparing MRI with TAB and clinical diagnosis of GCA reported pooled sensitivities and specificities of 93% and 81%, and of 73% and 88%, respectively [15]. A normal MRI of the cranial arteries was strongly associated with a normal TAB, with a negative predictive value of 98% [16]. However, MRI should be performed within the first 5 days of glucocorticoids initiation to avoid a decrease in sensitivity, which may not be feasible in many centers. In addition, the high cost of MRI, the expertise required to interpret the results, and the potential for patients to experience adverse reactions to contrast media or claustrophobia may further limit the widespread use of this diagnostic modality [14].

If there is a clinical suspicion of LV-GCA, imaging of the extracranial arteries is mandatory. Fluorodeoxyglucose positron emission tomography (FDG-PET), usually combined with low-dose computed tomography (CT), is considered the first imaging test to assess luminal changes and arterial wall inflammation in extracranial vessels (Fig. 13.3), especially in large deep vessels where US assessment is not accurate [14]. Evidence supports the use of FDG-PET for its diagnostic value (sensitivity 67–76%, specificity 66–100%, compared with clinical diagnosis or TAB), its advantage in detecting concomitant PMR and its ability to identify alternative diagnoses, such as atherosclerosis, infection, or malignancy [15]. Limitations of PET-CT include high cost and radiation exposure. In addition, the latest EULAR guidelines recommend FDG-PET as an alternative to ultrasound for the assessment of cranial GCA, in the light of recent studies supporting its utility in the diagnosis of GCA [14]. MRI may be a valid alternative to FDG-PET in detecting early signs of vasculitis, particularly wall thickness and enhancement. Both MRI and CT can detect structural lesions such as stenoses, occlusions, and aneurysms, but CT is more accessible and takes less time to obtain images than MRI, although it exposes the patient to radiation [14].

A potential algorithm to diagnose cranial-GCA has been proposed by the British Society for Rheumatology guideline (Fig. 13.4), which is based on imaging and TAB in a complementary manner, taking into account the pre-test probability [17]. In a setting where imaging is readily available with the appropriate expertise, it may be the first modality of choice in patients with a high clinical suspicion of GCA. Depending

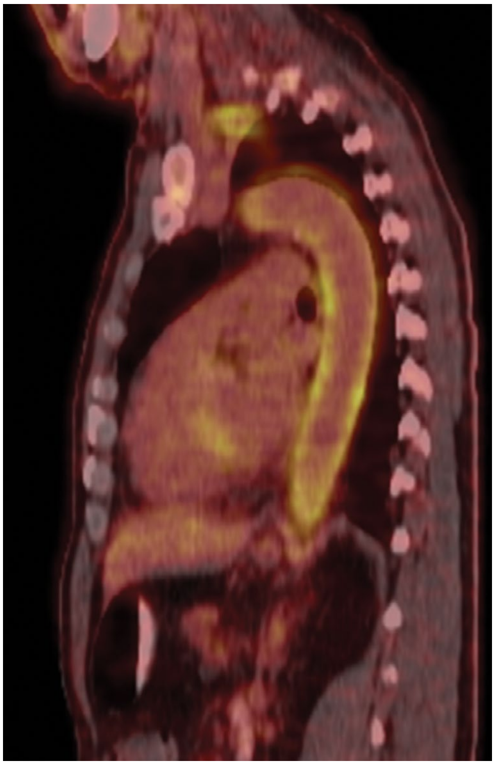
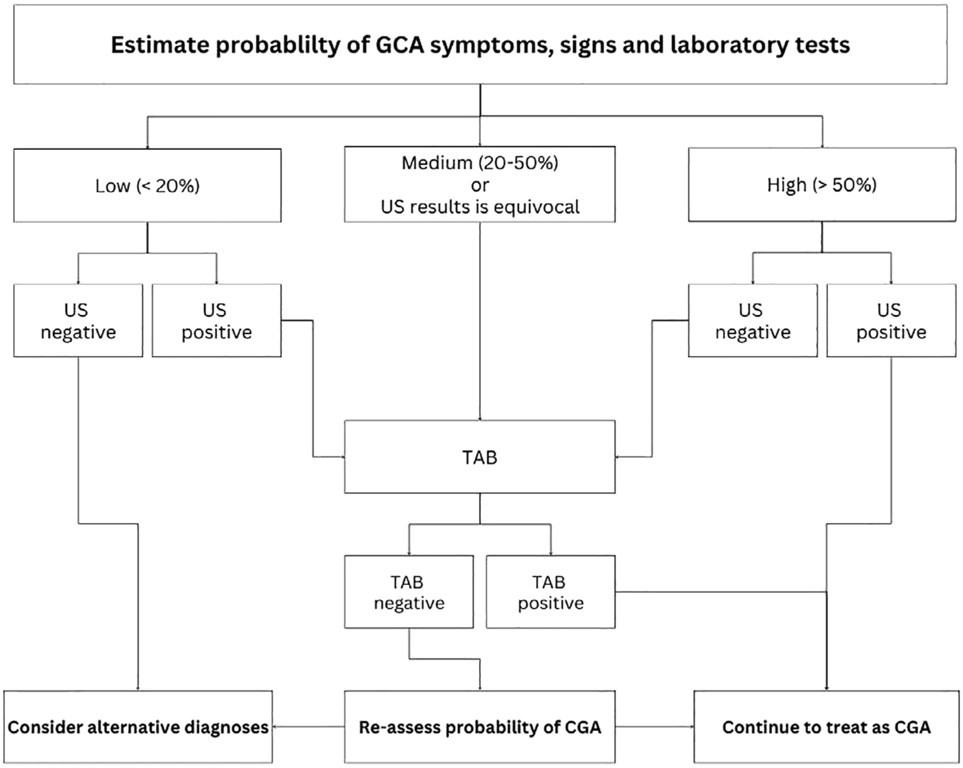


Fig. 13.3 Pathological fluorodeoxyglucose positron emission tomography (FDG-PET) revealing aortitis in suspected giant cell arteritis (GCA). This figure shows an FDG-PET image from a patient with GCA, highlighting pathological findings that indicate aortitis. The image demonstrates increased fluorodeoxyglucose uptake along the aortic wall, suggesting active inflammation within the aorta. The observed FDG avidity corresponds to regions of potential vascular involvement, particularly in the ascending and descending aorta

Fig. 13.4 Diagnostic algorithm for cranial-GCA proposed by the British Society for Rheumatology guideline [17]. *GCA* giant cell arteritis, *TAB* temporal artery biopsy, *US* ultrasound. In centers where Temporal Artery Biopsy (TAB) is performed rapidly and with a high expertise, an adaption of the proposed algorithm with TAB as the first test should be considered



Estimate probablilty of GCA symptoms, signs and laboratory tests
Low (< 20%)
Medium (20-50%) or US results is equivocal
High (> 50%)
US negative
US positive
US negative
US positive
TAB
TAB negative
TAB positive
Consider alternative diagnoses
Re-assess probability of CGA
Continue to treat as CGA

Abbreviations: CGA: Giant Cell Arteritis; TAB: Temporal Artery Biopsy; US: ultrasound on the imaging result, further testing (TAB or subsequent imaging) may be considered. In centers where imaging is not readily available and TAB is performed rapidly and with high expertise, an adaption of the proposed algorithm with TAB as the first test may be considered. In patients with suspected LV-GCA without cranial manifestations, the diagnostic approach is based on imaging. The choice of imaging modality depends on the clinical and practical context (accessibility, expertise in the technique, cost, etc.).

Treatment and Prevention

Cerebrovascular complications can be abrupt and irreversible, which is why GCA is considered a medical emergency and treatment should not be delayed once GCA is suspected.

Although the treatment has evolved in recent years, the cornerstone remains glucocorticoids (GC). Major guidelines recommend initiating treatment with high-dose oral GC (40–60 mg/daily of prednisone equivalent), preceded by intravenous (IV) pulse GC (250–500 mg IV pulse/day of methylprednisolone for 3 consecutive days) in the setting of manifestations of cranial ischemia (amaurosis fugax, visual loss, and stroke) [8, 17, 18]. The dose of GC should be slowly tapered to zero over 12–18 months, provided there is no recurrence of GCA symptoms, signs, or laboratory markers of inflammation [17, 18].

Among the non-glucocorticoid immunosuppressive agents, tocilizumab (TCZ) (162 mg SQ once weekly) or alternatively methotrexate (MTX) (10–20 mg SQ once weekly) is recommended as initial treatment in combination with GC in all patients [8], only in those at high risk of GC toxicity, or in refractory or relapsing patients [17, 18]. Data for other adjunctive therapies are either sparse (abatacept), from low-quality trials (ustekinumab, azathioprine, leflunomide, cyclophosphamide, dapsone, etanercept), or negative (adalimumab, infliximab, cyclosporine) [18].

Aspirin may be beneficial in preventing ischemic events in patients with vascular narrowing causing reduced cerebral blood flow, although there is no evidence from randomized clinical trials to determine the safety and efficacy of low-dose aspirin as an adjunctive treatment in GCA [8, 17].

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Polymyalgia Rheumatica

14

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Abstract

Polymyalgia rheumatica (PMR) is an immune-mediated inflammatory disease of unknown origin sharing pathogenetic and epidemiological features with giant-cell arteritis. The incidence of PMR increases after the age of 50 and it affects more frequently women. PMR is characterized by aching and morning stiffness in the cervical region and shoulder and pelvic girdles due to inflammation of periarticular structures of the glenohumeral and hip joints, mainly bursitis and tenosynovitis. Laboratory markers are non-specific but acute phase reactant levels are typically increased. Several imaging techniques, including ultrasound, magnetic resonance imaging (MRI), and positron emission tomography with computed tomography (PET-CT) can contribute to the diagnosis of PMR. Since several conditions can mimic PMR, this condition requires careful differential diagnosis. Oral glucocorticoids are the cornerstone of PMR treatment at initial daily doses of prednisone of 15 mg. Methotrexate and tocilizumab have shown efficacy in glucocorticoid-dependent or refractory cases. In 2012, European League Against Rheumatism/American College of Rheumatology preliminary classification criteria for PMR were proposed.

Keywords

Polymyalgia rheumatica · Giant-cell arteritis · Diagnostic criteria · Classification criteria · Glucocorticoids · Methotrexate · Tocilizumab

Polymyalgia rheumatica (PMR) is an immune-mediated inflammatory disorder of unknown origin characterized by aching and morning stiffness in the cervical region and shoulder and pelvic girdles [1]. Articular complaints are due to inflammation of periarticular structures of the glenohumeral and hip joints, mainly bursitis and tenosynovitis [1]. Glucocorticoids at low doses are associated with a prompt response of PMR symptoms [1]. PMR is closely related to giant-cell arteritis (GCA), a systemic large-vessel vasculitis, since both diseases affect patients older than 50 years and frequently occur together [1].

Epidemiology

The incidence of PMR increases with age, being uncommon before the age of 50. Women are approximately two to three times more likely to have PMR than men [2]. A geographical variation in the annual incidence of PMR shows the highest rates in persons from Scandinavian countries and northern European ancestry [2]. While in Denmark and Sweden, PMR annual incidence ranges from 34 to 68 cases per 100,000 in people aged 50 and older, in southern regions and other countries, PMR annual incidence is significantly lower (around 13 cases per 100,000 inhabitants/year in Italy and Spain, and 2 cases in Korea) [2, 3].

Compared with GCA, isolated PMR is two to three times more common. About half of patients with GCA present with concomitant PMR, and 5–15% of subjects with a presumably isolated PMR may have an associated GCA [4].

Pathogenesis

As for GCA, the etiology of PMR is still incompletely understood. However, PMR susceptibility and severity seem to be linked to the influence of environmental and genetic factors. Previous infections, vaccinations, and ultraviolet radiation exposure are among the environmental factors involved.

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Genetic associated factors include the ethnic background (since PMR predominates in patients from northern European latitudes), the existence of familial cases occasionally reported, and a genetic association with genes of the HLA complex [1].

Histopathology

Inflammatory lesions involving periarticular structures, such as bursae and synovium, are histologically characterized by mild inflammatory infiltrates with predominance of macrophages and T lymphocytes, mostly CD4+ helper T cells, with a limited presence of B cells [1]. These histological features are very similar to those found in the vascular lesions of giant-cell arteritis [1].

Clinical Manifestations

The clinical hallmark of PMR combines persistent pain with aching and morning stiffness in the neck, shoulder, and pelvic girdles lasting at least 30 min for at least 1 month [1]. Bilateral discomfort of the proximal limb and joint areas usually gets worse with movements of the affected area, usually radiates distally toward the elbows and knees, and typically interferes with usual daily activities, such as dressing, grooming, or combing [1]. Pain may be initially unilateral and tends to become bilateral. Where shoulder involvement prevails in the majority of patients (70–95%), the hips and neck are less frequently affected (50–70%) [1]. The main clinical features of PMR are illustrated in Table 14.1 [1, 5–7].

Nonerosive and asymmetric arthritis predominantly affecting the knees and wrists, tenosynovitis of the hands and wrists presenting as swelling and pitting edema, and carpal tunnel syndrome are distal articular manifestations present in about 50% of patients with PMR [1, 5] (Table 14.1). Swelling and pitting edema have been reported more frequently over the dorsum of the hands, wrists, ankles, and tops of the feet [5]. Tenosynovitis may also affect more prominently flexor tendons of the hands, but also extensor hand, peroneal, and posterior tibial tendons. Remarkably, some patients may present with isolated episodes of tenosynovitis after PMR diagnosis [5].

Fever, malaise or fatigue, anorexia, and weight loss are systemic manifestations accompanying in one-third of PMR patients at disease onset [1, 5–7]. Physical examination reveals limitation of active (but often also passive) movements of the shoulders due to pain, without evidence of swelling or tenderness of proximal joints [1].

Table 14.1 Main clinical and laboratory features of polymyalgia rheumatica [1, 5–7]

	Frequency (%)
Constitutional manifestations	
Malaise/fatigue	95
Morning stiffness	83
Weight loss	40
Fever	22
Depression	21
Shoulder girdle involvement	70–95
Hip girdle involvement	50–70
Neck involvement	50–70
Peripheral joint involvement	45
Arthritis (usually asymmetric)	25
Knee	10
Wrist	6
Metacarpophalangeal	8
Ankle	1
Carpal tunnel syndrome	14
Distal swelling with pitting edema	12
Distal flexor tenosynovitis	5
Laboratory markers	
Elevated ESR *(>40 mm/1st h)*	96
Elevated CRP *(>0.8 mg/dL)*	92
Thrombocytosis *(≥400,000 platelets/μL)*	40
Leukocytosis *(≥10,000 cells/μL)*	25
Anemia *(<10 g/dL)*	14
Elevated liver enzymes	
AST or ALT *(≥40 U/L)*	22
Alkaline phosphatase *(>120 U/L)*	51

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

Laboratory Findings

Laboratory findings are non-specific but elevated acute phase reactant levels, such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), are almost constant. Anemia of chronic disease, thrombocytosis, and leukocytosis are also present in a remarkable proportion of patients (Table 14.1) [1, 7]. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (aCCP) suggesting elderly onset rheumatoid arthritis, and antinuclear and other autoantibodies supporting the diagnosis of different systemic autoimmune diseases should be negative [1].

Imaging Techniques

Imaging techniques have become important tools in the diagnosis of PMR during the last years. These include conventional radiology (X-ray), ultrasound, scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), and 18-fluorodeoxyglucose positron emission tomography combined with CT (FDG-PET/CT). The choice of the radiologic technique often depends on availability and local expertise. The purpose of imaging studies in PMR is mainly to confirm the diagnosis, but also to rule out other conditions mimicking polymyalgic symptoms, comorbidities, and possible coexistence of a large vessel vasculitis, such as GCA [8]. However, the definite role of imaging techniques in disease diagnosis and disease activity assessment has not been established yet.

Conventional X-ray has been particularly used in patients with suspected PMR and peripheral joint involvement. Contrary to conditions such as rheumatoid arthritis and chondrocalcinosis (in a calcium pyrophosphate deposition disease), arthritis in PMR is typically nonerosive. A study using technetium pertechnetate scintigraphy has shown baseline abnormal contrast enhancement in shoulders of most patients with PMR, with negative results in controls and patients after treatment. Although scintigraphy seems to be associated with a high sensitivity in this study, the spread use of new imaging techniques has made its use currently limited [8].

Ultrasonography has played an increasing role in PMR due to its ability to visualize both articular and periarticular structures. The most frequent ultrasound findings in PMR include bilateral involvement of subacromial/subdeltoid bursae (corresponding to bursitis), followed by tenosynovitis of the long head of the biceps, glenohumeral joint inflammation, hip synovitis, and trochanteric bursitis [8]. For PMR diagnosis, several ultrasound features have been identified with high sensitivity (although with low specificity), and these include subacromial/subdeltoid bursitis (96.3%) and biceps tenosynovitis (85.2%). In addition, ultrasonography has proved to be useful to monitor disease activity and treatment response in PMR, since compared to laboratory markers and clinical evaluation, this technique has a similar or better sensitivity in detecting residual disease activity [8]. Ultrasound is also useful in the study of conditions included in the differential diagnosis of PMR and diseases associated with PMR. In this regard, the study of the acromioclavicular joint may be useful in distinguishing better PMR from calcium pyrophosphate disease [8]. It is also useful in detecting vascular involvement in cases of PMR associated with GCA [9]. The relevance of an ultrasound assessment in PMR is reflected by the fact that an ultrasound of the shoulder and pelvic girdles searching for abnormalities in periarticular structures was included in the 2012 European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) provisional classification criteria for PMR [10].

MRI is more sensitive than ultrasound for visualizing pelvic girdle and hip articular and periarticular inflammatory lesions. A characteristic MRI pattern of extra-articular involvement, including entheses, bursae, and periarticular structures, has been described in PMR [8]. Peritendinous enhancement of the pelvic girdle tendons, adductor muscles at the pubic bone, and different extracapsular sites has been detected almost constantly by MRI in PMR patients [8]. In patients with new-onset and active PMR, MRI has also identified myofascial inflammation of the shoulder and pelvic girdles, which are absent in rheumatoid arthritis and spondyloarthropathies [8]. MRI on the hands and wrists has shown tenosynovitis of the wrist extensor tendons as the most prevalent lesions of PMR patients compared with controls. Hands tenosynovitis may be detected by MRI also as subclinical expression of PMR [8]. Compared to patients with rheumatoid arthritis, the thickness of the supraspinatus tendon and the severity of the rotator cuff tendinopathy have been reported significantly higher in patients with PMR, who also have shown more severe effusions in the shoulder joint, shoulder tendon sheath, and trochanteric bursa [8]. MRI has also usefulness in monitoring disease progression in PMR patients on glucocorticoid therapy [8].

FDG-PET/CT is useful in identifying large-vessel vasculitis and inflammatory lesions of periarticular and extra-articular synovial structures in patients with PMR [8, 11, 12]. Although PET/CT is not routinely recommended in PMR diagnosis due to its cost and variable availability, it can be extremely useful in confirming coexisting large-vessel vasculitis and distinguishing PMR from other conditions such as malignancy and other systemic immune-mediated syndromes, particularly in cases unresponsive or refractory to initial glucocorticoid treatment [11, 12]. Of note, approximately 20% of patients with apparently isolated PMR show large vessels inflammation on PET/CT [11]. Common PET/CT findings in active PMR include increased uptake in scapular girdle (glenohumeral synovia, subacromial/subdeltoid bursa (Fig. 14.1a, b), supraspinatus tendinitis and biceps synovia), pelvic girdle (trochanteric/ischial bursa and hip synovia (Fig. 14.1c)), interspinous areas of cervical and lumbar vertebrae, and knees (when present) [8, 11, 12]. In a study with 60 PMR patients, FDG uptake was observed in glenohumeral and sternoclavicular joints (88% each), spinous processes and greater trochanters (81% each), ischial tuberosities (69%), acromioclavicular joints (25%), and wrists and elbows (6% each) [8]. The sensitivity and specificity of PET-CT in PMR diagnosis depend on the number and location of the sites with increased FDG uptake. A systematic review and meta-analysis on the diagnostic value of PET/CT in PMR patients found the highest diagnostic sensitivity (85%) when the FDG uptake affected the ischial tuberosity and greater trochanters, while the highest specificity (81%) was found in the interspinous processes FDG uptake [12].

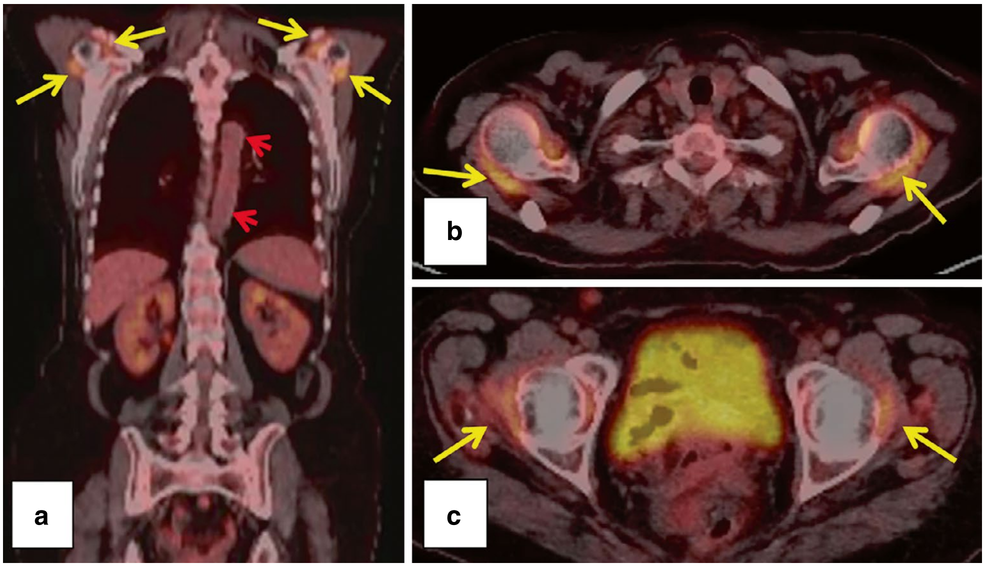

Fig. 14.1 ^{8}F-fludeoxyglucose positron emission tomography and computerized tomography (PET/CT) in a 63-year-old patient diagnosed with polymyalgia rheumatica, showing hypermetabolic activity of bursae, suggesting bursitis, of shoulders (arrows) (**a**, **b**) and hip joints (arrows) (**c**). No signs of inflammatory involvement of the aorta (short arrows) were observed and a large vessel vasculitis was ruled out (**a**)

Diagnosis

The diagnosis of PMR is usually achieved within 2–3 months after the onset of symptoms [1]. No specific clinical, biochemical, or immunological parameters can be used for diagnosing PMR. The diagnostic process is usually more complicated because a remarkable number of diseases mimicking PMR symptoms have to be included as potential differential diagnoses.

PMR may also coexist or be a part of a GCA, especially if symptoms suggestive of temporal arteritis symptoms are present. Approximately 50% of patients with GCA experience PMR symptoms [4]. Although PMR symptoms occur simultaneously with GCA symptoms in most patients GCA patients [13], PMR may be the first manifestation of GCA in about 20–40% of cases. Indeed, PMR may also constitute the only clinical manifestation of GCA in 4–15% of patients depending on the series [4], or up to 20% in studies using PET/CT in patients with apparently isolated PMR [11]. Despite all these facts, a temporal artery biopsy cannot be currently recommended in all patients with isolated PMR. Nevertheless, because patients with GCA presenting with apparently isolated PMR are at remarkable risk of developing ocular or neurological ischemic lesions, the detection of overt GCA symptoms in patients with previous isolated PMR symptoms must be pursued and patients diagnosed and treated promptly in order to avoid the potential occurrence of GCA-derived ischemic complications [4].

Differential Diagnosis

Different conditions affecting people over the age of 50 presenting with bilateral shoulder and/or pelvic girdle pain may mimic PMR [1, 14, 15]. The main diseases to be included in the differential diagnosis of PMR and their main characteristics are listed in Table 14.2.

Diagnostic and Classification Criteria

Since 1979, different diagnostic criteria have been proposed by different authors, and included clinical features (age at disease onset, joints involved, and duration of morning stiffness), laboratory parameters (ESR and CRP values), exclusion of mimicking diseases, and response to glucocorticoids (Table 14.3) [16].

In order to homogenize patients with PMR to be included in investigational studies, in 2012, a EULAR/ACR expert panel proposed provisional criteria for PMR classification based on a scoring system with both clinical and laboratory features, and the possibility to use ultrasound. When only clinical and laboratory parameters were used, a score of ≥4 provided a sensitivity of 68% and specificity of 78%. When ultrasound results were assessed, a score of ≥5 provided a sensitivity of 66% and a specificity of 81% (Table 14.4) [10].

Table 14.2 Differential diagnosis of polymyalgia rheumatica [1, 14, 15]

Disease	Differential diagnosis
Elderly-onset rheumatoid arthritis	• Primarily affects the large joints such as the knee, ankle, and less often the shoulder and hip joints • Typical extra-articular manifestations (serositis, rheumatoid nodules, cutaneous vasculitis) • Positive aCCP/RF in most patients • Presence of synovitis on ultrasound or MRI (in aCCP negative cases)
Remitting, seronegative symmetrical synovitis with pitting edema (RS3PE)	• Onset with symmetrical small joint arthritis with edema of the hands and feet • Typically in elderly men
Chronic rotator cuff tendinopathy/trochanteritis	• Unilateral/bilateral pain in shoulders/hips (usually intense) • Often combined with symptoms of cervical osteoarthritis • Morning stiffness tends to be brief or absent • Normal acute phase reactants
Calcium pyrophosphate deposition disease (chondrocalcinosis)	• Older age at disease onset • Presence of tibiofemoral osteoarthritis, ankle, and proximal joint arthritis • Radiologic osteoarthritic changes in the hands and knees, and tendinous calcifications
Polymyositis	• Muscle weakness (prevails to stiffness and pain) • Extramuscular manifestations (lungs, skin, gastrointestinal tract, heart) • Elevated circulating muscle enzyme levels • Presence of myositis-specific autoantibodies
Systemic erythematosus lupus/spondyloarthropathies/primary systemic amyloidosis	• Age >50 years • Proximal joint pain • Other specific manifestations
Fibromyalgia	• Generalized pain • Younger age group of patients • Normal inflammatory parameters
Paraneoplastic syndrome	• Absence of response to glucocorticoids or rapid recurrence of symptoms directly after tapering of glucocorticoids
Drug-induced muscular pain/inflammation	• Weakness (no morning stiffness) and raised circulating creatine kinase levels • Chronic use of statins • Immune checkpoint inhibitors used in cancer therapy
Hypothyroidism	• Generalized aching, stiffness, and arthralgia • Slow relaxation of deep tendon reflexes • Elevated serum TSH levels
Hyperparathyroidism	• Proximal stiffness and aching • Hypercalcemia and elevated parathyroid hormone
Parkinson's disease	• Generalized stiffness and sometimes pain, with overt or subclinical neurological manifestations
Multiple myeloma/other hematological and solid malignancies	• Diffuse or localized pain • Constitutional symptoms • Hematological/focal abnormalities

aCCP anti-cyclic citrullinated peptide antibodies, *MRI* magnetic resonance imaging, *RF* rheumatoid factor, *TSH* thyroid-stimulating hormone

Table 14.3 Previous diagnostic criteria for polymyalgia rheumatica[a]

Criteria	Bird et al.—1979	Jones and Hazleman—1981	Chuang et al.—1982	Healey—1984
Age	>65 years	–	≥50 years	>50 years
Clinical involvement	– Bilateral shoulder pain and/or stiffness – Bilateral upper arm tenderness	Shoulder and pelvic girdle pain which was primarily muscular in the absence of true muscle weakness	Bilateral aching and stiffness involving two of the following areas: neck or torso, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs. Movements of involved joint areas accentuate the pain	Pain involving two of the following areas: neck, shoulders, and pelvic girdle
Duration of morning stiffness	>1 h	Presence	≥30 min (or after periods of inactivity)	>1 h
Onset of illness	<2 weeks duration	At least 2 months	At least 1 month	At least 1 month
ESR	≥40 mm/h	>30 mm/h	>40 mm/h	>40 mm/h
CRP	–	> 0.6 mg/dL	–	–
Exclusion of other diseases	–	Absence of objective signs of muscle disease, rheumatoid or inflammatory arthritis or malignant disease	Absence of other diseases that could explain the symptoms (except giant cell arteritis), such as active rheumatoid arthritis, lupus erythematosus or polymyositis, chronic infection, multiple myeloma, and Parkinson's disease	Absence of other diseases capable of causing the musculoskeletal symptoms
Response to glucocorticoids	–	Prompt and dramatic response to systemic glucocorticoids (no dose stated, although in the study, prednisone at 10–15 mg/day was prescribed)	(Considered a supporting diagnosis in some cases—see below)	Rapid response to prednisone (≤20 mg/day)
Others	Depression and/or loss of weight	–	In cases with typical musculoskeletal findings but borderline ESR elevation, the authors considered ESR before and after the illness for comparison or for other evidence to support the diagnosis, such as a rapid response to low-dose glucocorticoids or history of giant cell arteritis	–
Conditions for meeting diagnostic criteria	Three or more features required (sensitivity 92% and specificity 80%)	All criteria required	All criteria required	All criteria required

PMR polymyalgia rheumatica, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

[a] Adapted from [16]

Table 14.4 2012 EULAR/ACR preliminary classification criteria for polymyalgia rheumatica [10]

ABSOLUTE REQUIREMENTS	
• Age ≥50 years at the time of diagnosis	
• Bilateral shoulder aching	
• Abnormal C-reactive protein and/or erythrocyte sedimentation rate	
CLINICAL CRITERIA	
Morning stiffness >45 min	+2
Hip pain or limited range of motion	+1
Absence of rheumatoid factor or anti-cyclic citrullinated peptide antibodies	+2
Absence of other joint involvement	+1
ULTRASOUND CRITERIA	
At least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis	+1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis	+1
A score of 4 or more is categorized as polymyalgia rheumatica (PMR) in the algorithm without ultrasound and a score of 5 or more is categorized as PMR in the algorithm with ultrasound	

Treatment

The cornerstone of PMR treatment is oral glucocorticoid therapy [16]. A prompt response to glucocorticoids usually provides additional confirmation of PMR diagnosis [15, 16]. A systematic review analyzing 16 studies on PMR treatment with glucocorticoids (14 observational studies and 2 randomized trials) found that disease remission was achieved with prednisone at a dose of 15 mg/day in most patients [16]. However, up to 13% of patients still required higher initial doses to control symptoms, and they usually responded well to prednisone at 20 mg/day [16]. Because of the increased risk of relapse during tapering, reductions below 10 mg/day should preferably follow a slow prednisone tapering rate lower than 1 mg per month [16].

The 2015 EULAR/ACR recommendations for the management of PMR offered a wide initial prednisone dosage range (from 12.5 to 25 mg/day) [15]. The expert panel conditionally recommended methotrexate in addition to glucocorticoids, particularly in patients at high risk of relapse and/or prolonged therapy, and in cases with risk factors, comorbidities, and/or concomitant medications favoring the occurrence of glucocorticoid-related adverse effects [15]. In this regard, a systematic review on the use of glucocorticoid-sparing agents in PMR, including methotrexate, azathioprine, and infliximab, evidenced that only methotrexate, either orally or intramuscularly (preferably) was found effective in patients with newly diagnosed or relapsing PMR at a dose of at least 10 mg/week [16].

The 2023 EULAR/ACR treat-to-target recommendations in PMR included the following recommendations: (a) the treatment target of PMR should be remission (defined as the absence of clinical symptoms and systemic inflammation); (b) treatment selection in PMR should be based on disease severity and activity, presence of relevant comorbidities and potential predictors of outcome, and therefore treatment should be modified as needed during follow-up; (c) once remission is reached, it should be maintained with the minimal effective dose of medication (advising not to push to taper-off medication too quickly, since this strategy often results in disease relapses); in addition, glucocorticoids withdrawal may have a higher priority than discontinuing additional immunosuppressive drugs (when both drugs are used in combination); and (d) disease activity should be monitored regularly, every 1–4 weeks until remission has been achieved, and at longer monitoring intervals (e.g., between 3 and 6 months) in patients in stable remission on therapy [17]. In these recommendations it is expected that drug-free remission may be achieved in a proportion of PMR patients, which has been reported in about 30–60% of patients in observational studies [17].

There is limited data on the use of biologics in the treatment of PMR. The use of infliximab did not exert steroid-sparing properties in an Italian series of 51 newly diagnosed PMR patients [18]. However, in 2 recent French studies (a placebo-controlled randomized clinical trial with 101 patients and a retrospective series of 53 patients) with glucocorticoid-dependent PMR and active clinical and/or biological disease, treatment with mainly monthly intravenous tocilizumab led to a drastic decrease in glucocorticoid dose and remission of PMR [19, 20]. Despite these promising results, more information about which patients should be treated, treatment duration, and possible long-term adverse effects of tocilizumab and other potential biologic agents are still required in patients with PMR.

Conclusions

PMR is an immune-mediated inflammatory disease typically affecting persons older than 50 years and more frequently women that is characterized by aching and morning stiffness in the cervical region and shoulder and pelvic girdles caused by inflammatory changes of periarticular structures of the glenohumeral and hip joints, usually bursitis and tenosynovitis. Raised acute phase reactant levels are almost constant. Among imaging techniques, ultrasound, MRI, and PET-CT can detect periarticular abnormalities that may support the diagnosis of PMR. A wide differential diagnosis must always be considered. Initial low doses of oral glucocorticoids are enough to control diseases in most cases. However, in glucocorticoid-dependent or refractory cases, methotrexate and tocilizumab have shown good results. 2012 EULAR/ACR preliminary classification criteria for PMR are waiting to be updated.

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Takayasu Arteritis

15

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Abstract

Takayasu arteritis (TKA) is a primary systemic large-vessel vasculitis involving the aorta and its major branches, usually affecting young females. Vascular lesions are typically stenotic or occlusive, and relapses tend to be frequent. Clinical presentation is often heterogeneous with constitutional and musculoskeletal symptoms, and ischemic manifestations derived from the involvement of arteries of extremities and other territories. Aortic arch aneurysm rupture and congestive cardiac failure due to aortic insufficiency are the two main causes of death. Uncontrolled or unrecognized hypertension is associated with poor long-term cardiovascular prognosis. Erythrocyte sedimentation (ESR) levels can be misleading in TKA because of the lack of correlation with the progression of vascular stenoses. Among vascular imaging techniques in TKA, magnetic resonance imaging (MRI) and MR-angiography (MRA) study is considered the most useful test for initial diagnosis and routine sequential follow-up. Disease activity is assessed by the combination of clinical manifestations, elevated ESR, and changes in vascular imaging techniques. The treatment of choice is based on glucocorticoids and additional immunosuppressive agents, preferably methotrexate. However, in patients with TKA refractory to these first-line agents, tocilizumab and anti-TNF agents have been demonstrated to be good therapeutic options. Revascularization procedures should be performed when disease is quiescent (if possible). Among them, bypass with autologous vessel grafts has shown better long-term patency results than angioplasty and stent placement. The 1994 topographic classification of vascular lesions at angiography, the 2010 European League Against Rheumatism (EULAR)/Paediatric Rheumatology European Society (PRES)/Paediatric Rheumatology International Trials Organisation (PRINTO), and the latest 2022 American College of Rheumatology (ACR)/EULAR classification criteria, are all supportive in assessing diagnosis and disease extent.

Keywords

Takayasu arteritis · Takayasu's arteritis · Systemic vasculitis · Large-vessel vasculitis · Magnetic resonance imaging/angiography · Computed tomography angiography · Positron emission tomography · Glucocorticoids · Tocilizumab · Anti-TNF agents · Revascularization techniques

Takayasu arteritis (TKA) is a primary systemic large-vessel vasculitis involving the aorta and its main branches [1]. TKA has a chronic and relapsing course that leads most often to

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vascular stenotic or occlusive lesions, and less frequently evolves to dilation and aneurysm formation [1, 2].

Epidemiology

TKA is a rare disease occurring in patients of all races, but it affects most frequently Asian patients, with a prevalence of 30 cases per million in Japan. The estimated annual incidence worldwide ranges from 0 to 2.6 cases per million inhabitants. Females are affected up to ten times more often than males. Although the peak incidence is observed between 15 and 30 years of age, TKA may occur during childhood and after the fourth decade of life [2–4].

Etiopathogenesis

TKA is a vasculitis of unknown origin. Hormonal and genetic factors seem to play a role in its pathogenesis because of the predominance of young women, ethnic/geographic distribution, and familial clustering. Specific human leukocyte antigen (HLA) and other non-HLA loci appear to be important susceptibility loci in patients with TKA [4]. Vascular inflammatory infiltrates are composed of macrophages and T lymphocytes, such as cytotoxic T cells, gamma delta (γδ) T cells, and natural killer T cells [4]. Macrophages stimulate CD4+ T cells in a T helper type 1 (TH-1) response. T cells produce interferon-gamma (IFN-γ), which stimulates macrophages to synthetize mediators involved in the induction and amplification of the inflammatory response and tissue injury. These molecules include proinflammatory cytokines, such as tumor necrosis factor-alpha (TNFα), interleukin (IL)-6, and IL-17, chemokines and growth factors, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), and other proteins, including perforin and matrix metalloproteinases (MMP) [4].

Patients with TKA have increased TNFα serum levels and TNF mRNA in peripheral blood mononuclear cells compared to healthy individuals [4]. IL-6 serum levels correlate with disease activity in TKA patients [4]. The potential role in TKA pathogenesis of both cytokines is supported by the efficacy of TNFα and IL-6 blockade in refractory patients [4–6]. Although the role of B cells in TKA pathogenesis remains to be elucidated, circulating germinal center memory B cells and aortic wall B cells forming ectopic lymphoid aggregates have been found in patients with TKA [4]. In this sense, patients with refractory TKA have responded to rituximab, a B-cell-depleting agent [4, 7].

Clinical Manifestations

TKA is considered a stenosing disease since more than 90% of patients present with vascular stenoses. Dilation or aneurysms are detected in 17–25% of subjects [8, 9]. The average age at disease onset ranges from 25 to 40 years, with cases reported during the first and eighth decades. In a Japanese nationwide patient registry of 1372 patients with TKA, the median age has been found significantly higher in males (43.5 years) than in female patients (34 years) and clinical and angiographic features differed according to onset age and sex [3]. Clinical features also vary across different populations, as it is illustrated in Table 15.1 [2, 3, 8–13].

More than half of patients with TKA manifest nonspecific systemic features, such as fever, weight loss, malaise, myalgia, and arthralgia [8–11]. Vascular manifestations, present in about half of patients at diagnosis, depend on the location and severity of vascular lesions, and include claudication of the upper extremities (62%), loss or asymmetry of pulses (53–57%; mainly in the upper extremities), blood pressure discrepancy in extremities (53%), bruits (53%; mostly over carotid arteries), and hypertension (33%). Initial angiographic abnormalities affect the aorta in 79% of patients, with frequent involvement of subclavian (65%) and carotid (43%) arteries [8]. Of note, around 20% of patients can be diagnosed incidentally in a self-limited sustained remission phase not requiring any treatment [8].

Other manifestations are derived from neurologic, visual, cardiac, and pulmonary involvement. Neurologic manifestations, usually caused by stenoses of carotid or vertebral arteries, occur in more than 50% of patients, such as dizziness, lightheadedness, syncope, vertigo, and orthostatic symptoms. Headache is experienced by about half of patients [8, 10–12]. Severe ischemic manifestations, such as transient ischemic attack or stroke, are observed in 5–20% of patients (10% of them at disease-onset) [2, 8, 10–12]. Stroke has accounted for 9.5% of deaths in TKA [13]. Visual complications, such as amaurosis fugax and permanent blindness, have been reported in 12–30% of patients with TKA [2, 8, 10, 12]. TKA retinopathy is derived from critical stenoses of carotid arteries causing hypoperfusion of retinal and choroidal vessels with formation of small vessel dilation, microaneurysms, arteriovenous anastomoses, and neovascularization. It occurs in 14–33% of Asian patients [4]. Hypertensive retinopathy and glucocorticoid adverse events affecting eyes (e.g., glaucoma, cataract) are also common ocular problems in TKA. Cardiac manifestations, usually due to aortic regurgitation, occur in 25% of patients since the aortic root is the site most frequently affected by aneurismal disease [2, 8, 13]. Aortic arch aneurysm rupture and congestive cardiac failure due to aortic insufficiency (also favored by uncontrolled hypertension) are the two main causes of death in TKA [2, 8, 13]. Symptomatic inflammation of coronary and pulmonary arteries is rare [8]. Although lung involvement is asymptomatic in most patients,

Table 15.1 Clinical characteristics of patients with Takayasu arteritis at disease onset in different series

Clinical features (*at the time of disease onset*)	USA NIH [2] (%)	USA CCF [8] (%)	USA MC [10] (%)	Italy [9] (%)	Mexico [11] (%)	India [12] (%)	Australia [13] (%)	Japan [3][a] (%)
Number of patients	**60**	**75**	**126**	**104**	**107**	**106**	**272**	**1372**
Systemic manifestations								
Fatigue/malaise	33	55	54	60	56	–	10	12
Fever	22	35	29	40	18	–	10	35
Weight loss (>10%)	12	–	36	20	22	–	–	–
Arthralgia	11	25	35	30	53	5	10	–
Myalgia	3	18	19	25	–	–	–	16
Cardiovascular involvement								
Diminishing or absence of pulse in extremities	22	57	70	72	96	–	–	5
Blood pressure asymmetry of upper and lower limbs (>10 mmHg)	13	53	66	66	–	–	–	4
Vascular bruits	23	53	65	65	94	68	–	–
Carotid arteries	–	36	50	–	–	–	–	–
Subclavian arteries	–	13	50	–	–	–	–	–
Abdomen vasculature	–	15	14	–	–	–	–	–
Femoral arteries	–	15	14	–	–	–	–	–
Carotidynia	17	15	15	37	–	–	–	–
Extremity claudication	36	48	52	43	29	–	30	–
Hypertension (new onset)	17	28	38	40	72	52	77	4
Aortic valve regurgitation	8	24	–	–	–	–	22	–
Pericarditis/chest pain	–	8	39	–	–	–	0.3	–
Congestive heart failure	2	7	–	–	–	12	33	–
Angina pectoris	–	5	6	–	–	–	–	–
Dyspnea	–	–		–	72	26	–	4
Neuro-ophthalmic involvement								
Headache	18	52	45	29	57	44	–	8
Lightheadedness/dizziness	–	33	49	–	–	–	–	9
Visual aberrations *(blurring, scotoma, diplopia)*	10	12	–	–	–	12	–	3
Amaurosis fugax	–	4	16	–	–	–	–	–
Transient ischemic attack	–	3	11[b]	1	–	–	6	–
Stroke	5	5	11[b]	2	–	10	11	–

CCF = Cleveland Clinic Foundation, Cleveland, OH; MC = Mayo Clinic, Rochester, MN; NIH = National Institutes of Health, Bethesda, MD

[a] Information collected by patients in a Japanese nationwide registry

[b] 11% of patients suffered either amaurosis fugax or stroke

pulmonary vasculature is affected in >50% of cases on imaging studies. Lung manifestations may become apparent years later in about 25% of patients, such as hemoptysis, dyspnea, cough, or chest pain. In symptomatic patients, perfusion lung studies can mimic chronic thromboembolic disease [4].

Involvement of intestinal arteries is reported in 20–40% of patients, but most lesions do not cause symptoms [8]. Dermatologic lesions occur in about 28% of patients with TKA, mostly as erythema induratum and pyoderma gangrenosum [4].

Hypertension is the major cause of disease-related morbidity on TKA. It is present in 17–40% of American and European patients [2, 8–10], and in >50% of Mexican, Australian, and Asian patients [11–13]. Although hypertension is usually caused by renal artery stenosis (observed in 25–80% of patients) [8], it may also result from suprarenal aortic stenosis or decreased aortic compliance [4, 13].

Laboratory Findings

No laboratory or serologic tests are specific for TKA diagnosis [4]. Elevated acute phase reactants, mainly erythrocyte sedimentation rate (ESR), may be helpful in assessing disease activity. However, normal acute phase reactants do not assure disease remission in all cases, and in many patients, ESR values do not correlate with systemic symptoms or vascular progression on imaging studies [4].

New biomarkers of TKA activity have been investigated. Among them, circulating levels of MMP, specifically MMP3 and MMP9, have been associated with disease activity [4]. Circulating levels of pentraxin-3, a protein synthetized within the inflammatory infiltrates, have better correlation with disease activity than ESR or C-reactive protein (CRP) levels [4]. However, these potential biomarkers have not been validated to be routinely used yet.

Vascular Imaging Techniques

Catheter-directed angiography had been initially considered the gold standard for the diagnosis of TKA. This invasive study provides information about the luminal caliber and vessel shape, and also allows recording intravascular blood pressure measurements and provides opportunities for intervention (e.g., angioplasty) in case of critical vascular lesions [2]. However, it does not provide information about vessel walls nor differentiate between acute/active and chronic/inactive lesions. In addition, angiography entails several risks, such as arterial invasiveness, ionizing radiation, and contrast exposition [4].

Currently, noninvasive computed tomography angiography (CTA) and magnetic resonance imaging (MRI) with its two components, contrast-enhanced MRI and MR-angiography (MRA) (conventional and/or 3D reconstruction), evaluate vascular lumen and vessel wall with good diagnostic accuracy to effectively replace or complement intra-arterial angiography [4].

CTA can detect a thickened intimal layer during a (delayed) venous contrast phase as a low-attenuation ring between the outer aortic wall and the lumen, and it can be used as a marker of activity in TKA. During the follow-up, subsequent CT decreases on mural thickness are associated with good vascular response/progression [4]. MRI and MRA with contrast enhancement provide information about the vessel wall and artery lumen, respectively (Fig. 15.1a–c). Mural thickness and assessment of artery wall enhancement usually identify inflammation or edema, since post-contrast T1-weighted images with mural enhancement reflect an increase of vascularity or excessive leakage of contrast out of the vasa vasorum, probably associated with vessel wall inflammation. T2-weighted hyperintense signal correlates with mural edema due to acute inflammatory changes [4]. However, the presumed inflammatory changes by MRI may also correspond to vascular remodeling in an inactive phase or diffuse atherosclerosis [4]. Compared with MRI/MRA, the accuracy of intra-arterial angiography has shown 100% sensitivity and specificity for TKA diagnosis. In addition, MRA tends to overestimate vascular lesions as occlusions in 2% of abnormal segments [4].

2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography (18F-FDG-PET) combined with CT (PET-CT) is widely used for the diagnosis of large-vessel vasculitis, mainly TKA, GCA, and other forms of aortitis (Fig. 15.1d–f) [4]. PET-CT is particularly useful to improve diagnostic precision, mainly in those patients with vasculitis presenting with constitutional symptoms and no clear vascular manifestations. Given its cumulative radiation exposure, during the follow-up, PET-CT should be reserved to those cases in whom a disease relapse is suspected with previous unsupportive clinical, laboratory, and conventional imaging (CT or MR) results, and when other potential causes have to be ruled out. However, the accuracy of PET-CT for detecting low-grade relapsing disease in untreated or treated

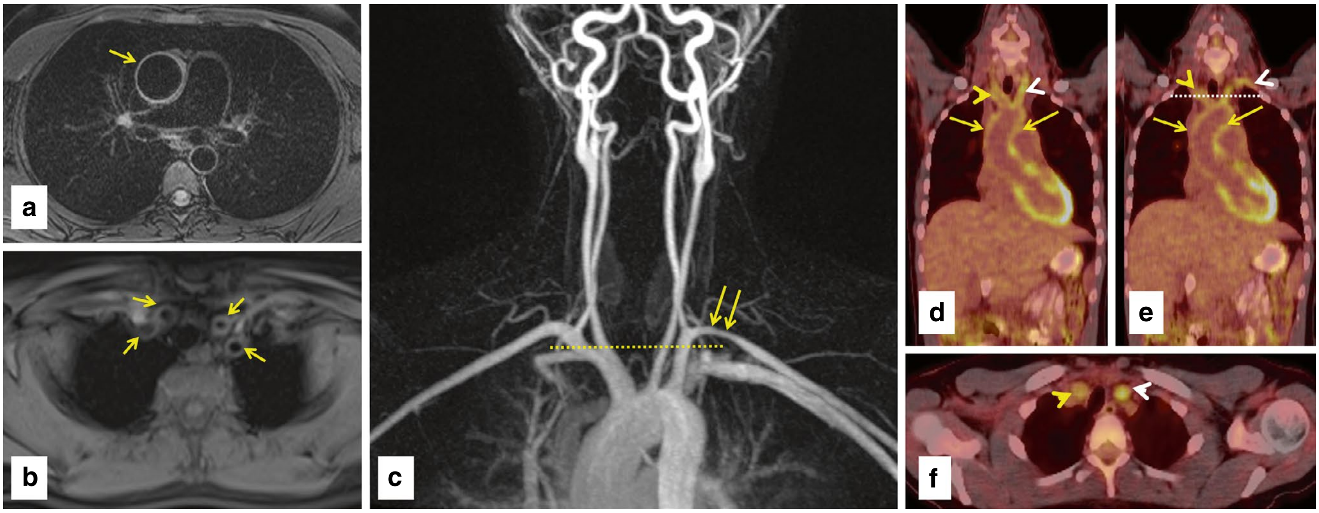

Fig. 15.1 Arterial lesions in a 23-year-old woman with Takayasu arteritis at disease onset. (**a**) MRI with post-contrast T1-weighted sequence showing mural enhancement of the ascending aorta, without vessel wall thickness (15 mm); (**b**) MRI hyperintense signal in a T2-weighted sequence correlating with mural inflammatory changes with vessel wall thickening (up to 25 mm) of all supra-aortic vessels (arrows) in a section corresponding to the yellow dashed line from (**c**); (**c**) MRA of the aortic arch and supra-aortic trunks depicting stenosis in the left subclavian artery (arrows); (**d**) PET-CT scan showing intense FDG uptake of the ascending aorta (long arrows) and supra-aortic trunks; this section includes the brachiocephalic trunk (yellow arrowhead) and left proximal subclavian and vertebral arteries (white arrowhead); (**e**) Sequential PET-CT scan section showing FDG uptake in the brachiocephalic trunk (yellow arrowhead) and left proximal and distal subclavian artery (white arrowhead) (the white dashed line delineates the anatomical section for figure **f**); (**f**) PET-CT axial image showing hypermetabolic lesions and thickened artery walls of brachiocephalic trunk (yellow arrowhead) and left subclavian artery (white arrowhead)

patients is limited, since it can also reflect vascular remodeling, active fibrosis, or atherosclerotic lesions. In this sense, a study of 30 patients with TKA did not find differences between arterial wall FDG uptake and systemic inflammation or disease activity. However, arterial thickness correlated with maximum FDG standardized uptake values (SUVmax) [4].

Ultrasound is a noninvasive imaging technique visualizing vessel wall thickening (usually circumferential) of the main arteries in TKA. Ultrasound is of limited value in TKA for assessing thoracic aorta and requires appropriate technology and experienced radiologists to interpret results [4]. Contrast-enhanced ultrasonography has revealed excellent sensitivity (100%) and specificity (80%) to detect disease activity of the carotid arteries when compared to FDG-PET scan [4].

The 2018 EULAR recommendations for the use of imaging techniques in large vessel vasculitis, MRI/MRA is recommended as the first imaging test for TKA diagnosis, since it provides information about mural inflammation and/or luminal changes [14]. PET, CT, and/or ultrasound are recommended as alternative imaging modalities in patients with suspected TKA. Although imaging is not routinely recommended for patients with TKA in clinical and biological remission, in suspected relapses, imaging is considered of help to confirm or exclude them. However, in clinical practice, MRI/MRA has also become of choice for monitoring vascular progression in TKA (since most are young women), because, compared with conventional angiography and CT-angiography, MRI/MRA also warrants a better safety profile [4, 14]. PET-CT should be reserved for identifying active arterial wall inflammation in patients with TKA, but mainly in those subjects with uncertain inflammatory activity. Ultrasound can be used as alternative imaging test in patients with suspected TKA (with limited value in thoracic aorta), and also for evaluating structural damage long-term monitoring, mainly in carotid, axillary, subclavian, and lower limbs arteries [14]. Combinations of these techniques, such as MRI/MRA or CTA with PET, are being used with promising results [4].

Histopathology

Biopsies of large arteries are usually not feasible. However, arteries are recommended to be obtained for histologic examination when patients undergo surgery for vascular or cardiac complications [4]. In arteries from patients with TKA, histopathologic patterns have been described at different stages. Active lesions usually reveal granulomatous arteritis, with transmural inflammation and patchy destruction of the internal elastic lamina. Lymphoplasmacytic cells, multinucleated giant cells, and cytotoxic and γδ T lymphocytes predominate within the infiltrates, mainly in the media layer [4]. Healing lesions include variable degrees of intimal and adventitial fibrosis, and extensive scarring of the media [4]. This inflammatory reaction promotes myointimal hyperplasia development, with subsequent vessel wall thickening and luminal stenosis [4]. Destructive lesions in the muscular layer and elastic lamina may result in artery dilation or aneurysms, which occur more commonly in the aortic root and arch [4].

Disease Activity Assessment

No routine laboratory markers are specific for TKA diagnosis. Although in a remarkable proportion of patients, ESR values do not correlate with systemic symptoms or progression on imaging studies, increased ESR levels may be helpful in assessing disease activity in TKA [4, 8]. Sequential imaging studies in TKA have revealed disease progression (determined by the presence of new vascular lesions) in about half of patients presenting with asymptomatic disease and normal ESR values [4, 8]. Similarly, clinical evaluation may underestimate a subclinical activity, since almost 50% of patients with TKA undergoing vascular surgery in apparent clinical remission disclose histologic inflammation [2, 4].

In 1994, Dr. Gary Hoffman team (at the National Institutes of Health [NIH], Bethesda, Maryland) generated the criteria for assessing disease activity in TKA [2]. They are known as NIH criteria or Kerr criteria, and provide support to evaluate active disease according to the existence of new or worsening of any two or more of the following parameters: (1) Signs or symptoms of vascular ischemia or inflammation; (2) Increase in sedimentation rate; (3) Angiographic features; and (4) Systemic symptoms not attributable to another disease [2]. They have demonstrated to be specific and helpful when present. However, their absence does not assure disease remission. NIH criteria have been subsequently used in other TKA studies with similar utility in monitoring TKA activity and guiding treatment decision-making when used in conjunction with serial imaging modalities, which are currently preferred with MRI/MRA, followed by CTA or PET-CT [4].

Diagnosis

Because biopsies of the aorta or its main branches are usually impractical and there are no specific laboratory/serologic tests for TKA, its diagnosis is normally based on clinical features in the setting of vascular imaging abnormalities suggestive of arterial inflammation [4].

Associated or Underlying Disorders

TKA has been frequently associated with sarcoidosis and Crohn's disease, two systemic diseases characterized by granulomatous lesions [4]. Other diseases concomitantly reported with TKA include granulomatosis with polyangiitis (GPA), systemic lupus erythematosus, ulcerative colitis, and primary biliary cirrhosis [4].

Differential Diagnosis

The definite diagnosis of TKA is usually challenging, and even more difficult in those patients presenting with nonspecific features. The main differential diagnosis has to be performed with those systemic vasculitides in which the aorta and/or its major branches can be involved, mainly GCA, isolated aortitis, and immunoglobulin G4 (IgG4)-related disease (IgG4-RD) [4]. Aortic inflammation has also been described associated with other systemic vasculitides, such as GPA, Behçet's disease, and Cogan's syndrome, and to other systemic autoimmune diseases, such as rheumatoid arthritis, spondyloarthropathies, systemic lupus erythematosus, Sjögren's syndrome, and sarcoidosis [4]. Differential diagnosis of TKA must also include infectious diseases, such as syphilis, tuberculosis, and fungal infections, and hereditary vasculopathies or vascular collagenopathies, such as type IV (vascular form) Ehlers-Danlos syndrome, Marfan syndrome, Loeys-Dietz syndrome, and fibromuscular dysplasia [4]. Of note, vessel involvement of infections and collagenopathies is characterized by dilations, aneurisms, and vascular tortuosity, and stenotic lesions are usually absent.

GCA merits special attention in TKA differential diagnosis, since both large vessels vasculitis are characterized by granulomatous infiltrates and giant cell formation. GCA affects mostly Caucasian patients older than 50 years, with a female predominance (2:1). GCA typical clinical features overlapping with TKA include headache and visual and neurological ischemic events, mostly amaurosis [4]. In GCA, the aorta and its main branches occur in up to two-third of patients, and vascular territories involved are similar to those described in TKA. However, in GCA stenotic vascular lesions at diagnosis-onset and during the follow-up occur in only 3% and 6% of patients, respectively [4]. Therefore, GCA has to be suspected in patients older than 40–50 years without overt stenotic vascular lesions.

Classification and Angiographic Criteria

The 2012 International Chapel Hill Consensus Conference (CHCC) on the nomenclature of vasculitides defined TKA as a large vessel arteritis, often granulomatous, predominantly affecting the aorta and/or its major branches, with a disease onset usually in patients younger than 50 years [1].

The 1990 American College of Rheumatology (ACR) criteria for the classification TKA proposed the next parameters: (1) age at disease onset ≤40 years; (2) claudication of extremities; (3) decreased brachial artery pulse; (4) blood pressure difference between both arms of >10 mmHg; (5) bruits over subclavian arteries or aorta; and (6) arteriographic abnormalities. A patient could be classified with TKA if 3 out of 6 criteria were fulfilled, with 90.5% sensitivity and 97.8% specificity [15]. The 1990 ACR criteria were replaced by the 2022 ACR/European League Against Rheumatism (EULAR) classification criteria for TKA, which initially required the diagnosis of medium- or large-vessel vasculitis and the exclusion of other potential causes or mimickers

Table 15.2 2022 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Classification Criteria for Takayasu Arteritis [16]

Considerations when applying these criteria	
These classification criteria should be applied to classify the patients as having Takayasu arteritis when a diagnosis of medium-vessel or large-vessel vasculitis has been made	
Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria	
Absolute requirements	
Age ≤60 years at the time of diagnosis	
Evidence of vasculitis affecting the aorta or its main branches by imaging[a]	
Additional clinical criteria	
Female sex	**+1**
Angina or ischemic cardiac pain	**+2**
Arm or leg claudication	**+2**
Vascular bruit (over the aorta, carotid, subclavian, axillary, brachial, renal or iliofemoral arteries)	**+2**
Reduced pulse in upper extremity (of axillary, brachial, or radial arteries)	**+2**
Carotid artery abnormality (reduction or absence of pulse or tenderness on palpation)	**+2**
Systolic blood pressure difference in arms ≥20 mm hg	**+1**
Additional imaging criteria	
Number of affected arterial territories (stenosis, occlusion or aneurysm)[b]	
• 1 arterial territory	**+1**
• 2 arterial territories	**+2**
• ≥3 arterial territories	**+3**
Symmetric involvement of paired carotid, subclavian, or renal arteries	**+1**
Abdominal aorta involvement and either renal or mesenteric involvement	**+3**
Sum the scores for 10 items, if present. A score of ≥5 points is needed for the CLASSIFICATION OF TAKAYASU ARTERITIS	

[a] Vascular abnormalities by imaging (computed tomography, catheter-based, magnetic resonance angiography, ultrasound, positron emission tomography)

[b] Select one (1, 2, or ≥3 arterial territories affected) among the following 9 territories: thoracic aorta, abdominal aorta, mesenteric, left or right carotid, left or right subclavian, left or right renal arteries

[16]. The final 12 criteria items and their weights are listed in Table 15.2. A score ≥5 points is needed for classifying a patient with TKA [16].

Classification criteria for TKA in children were also delineated in the 2010 updated consensus for common childhood vasculitides by the EULAR, the Paediatric Rheumatology European Society (PRES), and the Paediatric Rheumatology International Trials Organisation (PRINTO) [17]. TKA classification in children requires typical angiographic abnormalities of the aorta or its main branches and pulmonary arteries (mandatory criterion) plus one of these five criteria: (1) decreased peripheral pulse or claudication; (2) blood pressure discrepancy higher than 10 mmHg in any limb; (3) bruits on the aorta or its major branches; (4) hypertension; and (5) elevated acute phase reactants [17].

Previous angiographic TKA classifications were updated at the 1994 Takayasu Conference (Tokyo, Japan), by Hata et al. [18]. Four angiographic types were defined according to vascular topographic distribution/involvement: (a) Type I: primary branches of the aortic arch; (b) Type IIa: ascending aorta, aortic arch, and its branches; (c) Type IIb: ascending aorta, aortic arch with its branches and thoracic descending aorta; (d) Type III: thoracic descending aorta, abdominal aorta and/or renal arteries; (e) Type IV: abdominal aorta and/or renal arteries; and (f) Type V: a combination of features of both type IIb and IV. In addition, the involvement of coronary or pulmonary artery should be indicated as C (+) or P (+), respectively [18].

Treatment

Pharmacological Management Glucocorticoid therapy results in clinical improvement in almost all patients, and leads to remission in up to 90%. However, most patients suffer relapses while prednisone is reduced <20 mg/day [4, 8], and additional immunosuppressive therapy is required. Methotrexate has been effective in patients with relapsing or glucocorticoid-dependent disease [4]. Other conventional immunosuppressive drugs, such as azathioprine, leflunomide, and oral cyclophosphamide, have been useful in controlling disease activity [4]. However, glucocorticoid reduction or discontinuation is still difficult despite the concomitant use of cytotoxic agents, since relapses still occur in most patients [4].

The use of biologic immunosuppressive agents targeting different proinflammatory cytokines in TKA, such as TNF (from 2004) [5] and IL-6 (from 2018) [19], has brought dramatic progress in the management of patients with TKA, mostly in those with refractory or relapsing disease, since their higher effectiveness in controlling disease activity with clearly less side effects compared to glucocorticoids and other conventional immunosuppressive agents. Tocilizumab use in TKA has been evaluated in 2 clinical trials including relapsing and newly diagnosed patients with TKA, with weekly subcutaneous (162 mg) and monthly intravenous (8 mg/kg) administration, respectively [20, 21]. The results corroborated the efficacy of tocilizumab as an effective steroid-sparing agent in TKA. Although maintenance therapy is still necessary, monthly intravenous administration is associated with prolonged remission rates than subcutaneous tocilizumab [22]. An international multicenter retrospective study of 209 patients with refractory TKA treated with anti-TNF agents and tocilizumab evidenced similar efficacy, relapse, and drug retention rates for both therapies [6].

The possible role of B cells in the pathogenesis of TKA has been explored, leading to use of B-cell depletion therapy with rituximab, a chimeric anti-CD20 monoclonal antibody, in several refractory patients with TKA, with effectiveness in most of them [7]. However, the real efficacy of rituximab needs further validation in controlled clinical trials [7].

While other biologics and small molecules, such as ustekinumab and tofacitinib, have been sporadically reported with good results, abatacept was not useful in reducing relapses in a randomized placebo-controlled trial [4]. Autologous hematopoietic stem cell transplantation has been demonstrated to be useful in refractory TKA, as reported in a series of six patients with TKA [4].

The use of aspirin and statins in TKA patients does not seem to protect from the development of ischemic vascular complications nor in reducing relapses or progression of arterial lesions [4]. Therefore, the role in primary or secondary vascular prophylaxis with antiplatelet agents or statins in TKA is still pending to be validated.

Endovascular and Surgical Management About half of patients with TKA require vascular revascularization procedures despite medical treatment. Interventional procedures are indicated in symptomatic cervicocranial or coronary artery disease, renal artery stenosis leading to renovascular hypertension, aortic aneurysm with risk of dissection or rupture, severe extremity claudication and moderate to severe aortic valve regurgitation or aortic coarctation [4]. Revascularization procedures include percutaneous transluminal angioplasty (PTA), with or without stent placement, and surgical placement of synthetic grafts or autologous vessel bypass, as well as aortic root repair or aortic valve replacement for aortic insufficiency [4]. In general, surgical revascularization procedures, especially with autologous vessels, tend to have better results than angioplasty and stenting [4], and angioplasty provides better patency rates than stent placement [4]. Endarterectomy is not recommended due to the increased risk of vessel rupture since arterial lesions can be rigid and often involve the entire vessel wall thickness. Revascularization procedures in TAK ideally should be performed during disease remission [4].

Recognition and treatment of hypertension in patients with TKA is crucial. Because of the high frequency of subclavian arteries and brachiocephalic trunk stenoses resulting in falsely low peripheral blood pressure readings, detection of hypertension is often delayed [2, 4, 8]. Therefore, vascular repair of the stenotic artery lesions in extremities to better determine blood pressure and revascularization of renal artery stenoses causing hypertension have to be prioritized in TKA.

Conclusions

TKA is a primary systemic large-vessel vasculitis involving the aorta and its major branches, usually affecting young females. Its diagnostic process is often difficult since TKA heterogeneous presentation with systemic manifestations and vascular involvement of different territories. Although stenotic and occlusive lesions prevail, aortic arch aneurysm rupture and congestive cardiac failure due to aortic insufficiency are the two main causes of death. Uncontrolled or unrecognized hypertension is associated with poor long-term cardiovascular prognosis. Among vascular imaging studies, MRI/MRA is the most useful technique for initial diagnosis and routine sequential follow-up. TKA treatment of choice is based on glucocorticoids and additional immunosuppressive agents, preferably methotrexate. Lately, tocilizumab and anti-TNF agents have demonstrated efficacy in treatment-naïve and relapsing patients. Revascularization procedures should be performed when disease is quiescent. Among them, bypass with autologous vessel grafts have shown better long-term patency results than angioplasty and stent placement.

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16

Polyarteritis Nodosa

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Abstract

Polyarteritis nodosa (PAN) is a medium-sized vessel primary or idiopathic systemic necrotizing vasculitis in which small vessels are not affected and anti-neutrophil cytoplasmic antibodies (ANCA) are not present. Hepatitis B virus and other viral infections may cause vascular lesions, clinically and histologically indistinguishable from PAN. Clinical manifestations of PAN are widespread and heterogeneous. Peripheral nerves and skin are the most frequently affected tissues. However, gastrointestinal tract, kidney, heart, and central nervous system involvement is associated with a worse prognosis. When biopsies of involved tissues are negative for vasculitis or cannot be obtained, visceral angiography may support the diagnosis of PAN if micro-aneurysms and/or stenotic arterial lesions are evidenced. Treatment strategies include high-dose glucocorticoids in combination with additional immunosuppressive agents in severe cases, particularly intravenous cyclophosphamide. After the 1990 American College of Rheumatology (ACR) classification criteria for PAN, the categorization of ANCA-associated vasculitides and infection-associated vasculitides as conditions different from PAN, as well as the recent discovery of monogenic autoinflammatory diseases presenting with PAN-like phenotypes, such as deficiency of adenosine deaminase 2 (DADA2) and vacuoles, E1 enzyme, X-linked, auto-inflammatory, somatic (VEXAS) syndrome, have all contributed to unveil the real rarity of PAN.

Keywords

Polyarteritis nodosa · Vasculitis · Diagnosis · Classification · Treatment

Polyarteritis nodosa (PAN) is a primary or idiopathic systemic necrotizing vasculitis involving medium-sized vessels, typically small to medium-sized muscular arteries ranging from 300 μm to 1 cm in diameter [1–3]. Small vessels, including arterioles, capillaries, and postcapillary venules, are not affected, and therefore, glomerulonephritis or pulmonary capillaritis are not features of PAN [1, 2]. Anti-neutrophil cytoplasmic antibodies (ANCA) are absent. PAN is indistinguishable from secondary vasculitis triggered by hepatitis B virus (HBV) (known as HBV-associated vasculitis) and other infectious agents. Malignancies and monogenic autoinflammatory diseases have been also associated with secondary forms of PAN [4, 5]. PAN-type lesions may be also confined to specific organs or systems, being part of a different category, single-organ vasculitis [6].

Epidemiology

PAN is a rare disease that over time has become almost ultra-rare. While before the 1990 decade, more than a third of patients with PAN were infected by HBV, after HBV vaccination, less than 5% of patients with PAN or PAN-like vasculitis in developed countries are HBV-associated vasculitis [7]. After widespread HBV vaccination campaigns in the 1990 decade, followed by the exclusion of secondary cases of PAN and the inclusion of ANCA-associated vasculitis as

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different vasculitis types in the 1994 Chapel Hill Consensus Conference (CHCC) for the Nomenclature of Systemic Vasculitides [2], the annual incidence of PAN drastically decreased and now ranges from 0 to 2 cases per million inhabitants in European countries [8, 9], with a prevalence ranging from 2 to 30 cases per million inhabitants [7, 8]. However, the latter values were still higher because of the inclusion of a considerable proportion of patients infected with HBV [7].

Pathogenesis

Etiopathogenesis of PAN is still poorly understood. Because previous experimental animal models had proved the development of necrotizing arteritis mediated by immune complexes, PAN was initially thought to be caused by this mechanism [3]. In addition, PAN-like lesions associated with HBV and other chronic viral infections, such as HCV, HIV, cytomegalovirus, parvovirus B19, and human T-lymphotropic virus type I, were also triggered by immune complexes [3]. However, circulating immune complexes, complement consumption, and glomerulonephritis, all of the features characteristic of immune-complexes mediated lesions, are not present in PAN [2]. The presence of dendritic cells and the abundance of CD4+ lymphocytes in artery infiltrates suggest that antigen-specific T-cell-mediated immune responses may also play a role in the pathogenesis of vascular inflammation in PAN [3].

Clinical Manifestations

Clinical manifestations of PAN are diverse and widespread since arteries may be affected throughout the body causing tissue ischemia or hemorrhage derived from vessel occlusion or rupture, respectively. The course of the disease varies from indolent and subclinical presentations to acute and life-threatening disease forms. Clinical features of PAN include common but non-specific constitutional symptoms such as malaise, weight loss, fever, arthralgia, and myalgia, and manifestations derived from damage or dysfunction of the affected organs (Table 16.1) [3, 4, 10].

The peripheral nervous system and the skin are the territories more frequently involved. Mononeuritis multiplex is the most common neurological manifestation followed by stroke and symmetrical polyneuropathy [3, 4, 10]. Cranial nerve palsy is described in less than 2% of cases. Cutaneous involvement is present in more than half of patients as subcutaneous nodules, necrotic lesions, and livedo reticularis. Purpuric lesions, distal digital ischemia, and Raynaud phenomenon occur less frequently [3, 4]. Gastrointestinal manifestations of PAN are also common and often associated with a poor prognosis [4, 10, 11]. When present, these include nausea/vomiting (32%), diarrhea (16%), hematochezia/melena (5%), hematemesis (8%), ulcerations of esophageal (13%), gastroduodenal (32%), and colorectal (5%) territories. About a third of patients may require surgery [11]. Renal involvement in PAN consists of tissue infarction or hematomas, usually produced by rupture of renal microaneurysms [3]. Kidney infarcts may be clinically silent or produce any degree of hematuria and mild to moderate proteinuria. Glomerulonephritis is not a feature of PAN. Renal insufficiency secondary to multiple renal infarcts and hypertension secondary to intrarenal artery involvement are less common [3, 4, 10].

Compared to PAN, HBV-associated vasculitis entails a more severe disease with a higher frequency of peripheral neuropathy, hypertension, cardiomyopathy and testicular involvement, and less cutaneous lesions [10]. Other secondary forms of necrotizing vasculitis (e.g., those associated with other infections, hematologic and solid malignancies, and autoinflammatory diseases, such as deficiency of adenosine deaminase 2 [DADA2] and vacuoles, E1 enzyme, X-linked, auto-inflammatory, somatic [VEXAS] syndrome), may be clinically and histologically indistinguishable from PAN [4].

Table 16.1 Principal manifestations in patients with PAN[a]

Clinical manifestations	PAN (%)	HBV-associated vasculitis (%)	Other secondary vasculitis (%)
Men/women ratio	1.6–1.8	2.1	1.3
Age at diagnosis; mean ± SD years	51–54 ± 17–18	52 ± 16	54 ± 21
Systemic features			
Fever	54–60	70	56
Weight loss	53–66	76	42
Myalgia	37–62	53	29
Arthralgia	45–47	52	53
Cutaneous	58–60	35	56
Nodules	24–36	6	–
Necrosis	40	–	42
Livedo reticularis	16–20	11	20
Purpura	16–24	18	7
Distal ischemia	12–13	14	–
Neurological	60–74	88	62
Mononeuritis multiplex	42–64	82	36
Polyneuropathy	6	–	7
Central nervous system—stroke	5–9	4	11
Gastrointestinal (GI) tract	28–31	50	26
Abdominal pain	22–28	50	26
GI bleeding	4–11	3	11
GI perforation	4–6	6	7
Cholecystitis	2	7	–
Appendicitis	1	2	–
Pancreatitis	3	6	–
Surgical abdomen	11	20	–
Renal	23	15	13
Acute kidney injury	6	–	4
Proteinuria	12–20	24	6
Hematuria	15	15	–
Hypertension	18–27	49	11
Cardiac	9–20	26	11
Cardiomyopathy	4–6	13	6
Pericarditis	5	7	–
Eye	8	11	13
Retinal vasculitis/exudates	4	6	–
Pulmonary	6–7	5	9
Cough	6	5	–
Pleural effusion	3	4	–
Lung infiltrates	4	2	–
Testicles—orchitis/epididymitis	13–16	24	16

HBV hepatitis B virus, *PAN* polyarteritis nodosa

[a] From [4, 10]

Laboratory Features

There are no laboratory abnormalities specific for PAN. Elevated erythrocyte sedimentation rate and C-reactive protein levels, and chronic anemia and leukocytosis are frequently present [3]. Hypereosinophilia may be occasionally observed but, when present, clinical features of eosinophilic granulomatosis with polyangiitis (EGPA) must be ruled out. The presence of ANCA strongly suggests the diagnosis of other systemic necrotizing vasculitis associated with these antibodies, such as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), or EGPA [3, 9]. Serologies for HBV, HCV, and other chronic viral infections are useful to diagnose viral-associated vasculitis [3]. In some cases, particularly in those patients with PAN refractory to conventional immunosuppressive therapy lines, biochemical and hematological markers for cancer and genetic analyses for autoinflammatory diseases, such as DADA2 and VEXAS syndrome, have to be investigated [5].

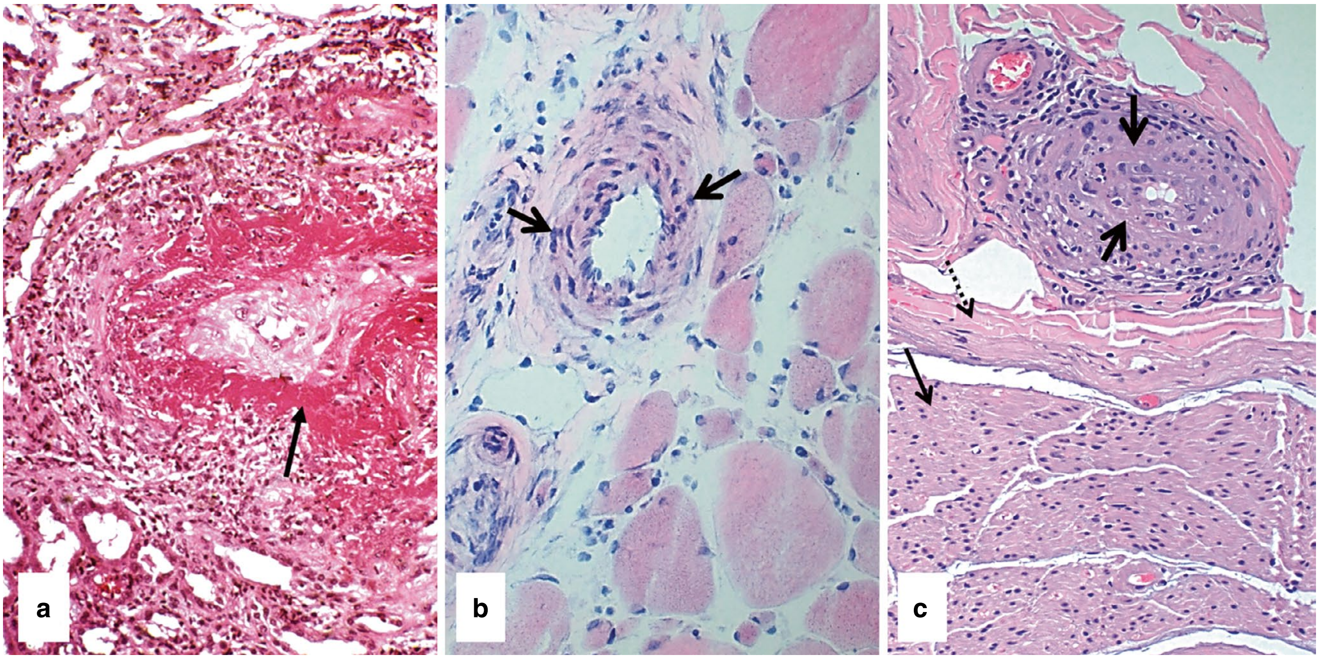

Fig. 16.1 Histopathologic findings in polyarteritis nodosa. (**a**) Medium-sized artery with mixed inflammatory infiltrates and fibrinoid necrosis (arrow). (**b**) Muscle biopsy showing lymphocytic vasculitis in a small-sized artery (arrows). (**c**) Sural nerve biopsy (from the same patient that **b**) disclosing a dense inflammatory reaction with fibrinoid necrosis (short arrows) in a medium-sized artery outside the perineurium (dashed arrow) and the nerve fibers (narrow arrow)

Histopathological Findings

Vascular inflammatory lesions of PAN have a characteristic patchy and segmental distribution [3]. Inflammatory infiltrates are composed of lymphocytes, macrophages, and variable numbers of neutrophils and eosinophils [3]. Granulomas and giant cells are usually absent. Fibrinoid necrosis is commonly seen in active lesions, and neutrophils are more often present in vessels with fibrinoid necrosis [3] (Fig. 16.1). At later stages, lymphocyte and macrophage infiltration usually predominates and neoangiogenesis becomes apparent [3]. In advanced lesions, vascular remodeling and healing processes lead to the development of intimal hyperplasia and diffuse fibrotic changes within the vessel wall. Thrombotic phenomena may also contribute to vascular occlusion. Severe vessel wall damage may result in the typical formation of microaneurysms. Different stages of the same inflammatory process (e.g., acute necrotizing and fibrotic or healing lesions) may coexist in different artery segments [3].

Diagnosis

Biopsy Findings

In an appropriate clinical setting, the diagnosis of PAN can be obtained by proving vascular inflammation in medium-sized or small arteries. Overall, the performance of biopsies in symptomatic territories (e.g., skin, muscle, peripheral nerve, gastrointestinal tract or testicle) optimizes the diagnostic yield to up to 70% [4]. In selected individuals in whom PAN is strongly suspected, muscular biopsies from clinically affected muscles may reveal vasculitis in 65–70% of patients, and combined muscle and nerve biopsies in symptomatic patients have been shown to provide histologic confirmation of vasculitis in 83% of them [10, 12]. In cases in which biopsies of muscle and nerve are blindly performed, vasculitis can be detected in up to one-third of patients [3, 12]. Testicular biopsies have a low diagnostic yield and should be only performed when testicles are clinically involved and biopsies from other symptomatic territories have been negative [3, 12]. Because of the potential risk of hemorrhagic complications, blind renal and liver biopsies should be avoided, or (if really needed) performed carefully under ultrasonography guidance by or after proving the absence of microaneurysms by angiographic techniques [3, 12]. PAN and other systemic necrotizing vasculitis can also be unexpectedly diagnosed in temporal artery biopsies from patients with clinical suspicion of giant-cell arteritis, usually when inflammation of the collateral vessels surrounding a spared temporal artery is observed. In these situations, PAN is more frequently associated with the presence of neutrophils and fibrinoid necrosis within the infiltrates of collateral vessels [13].

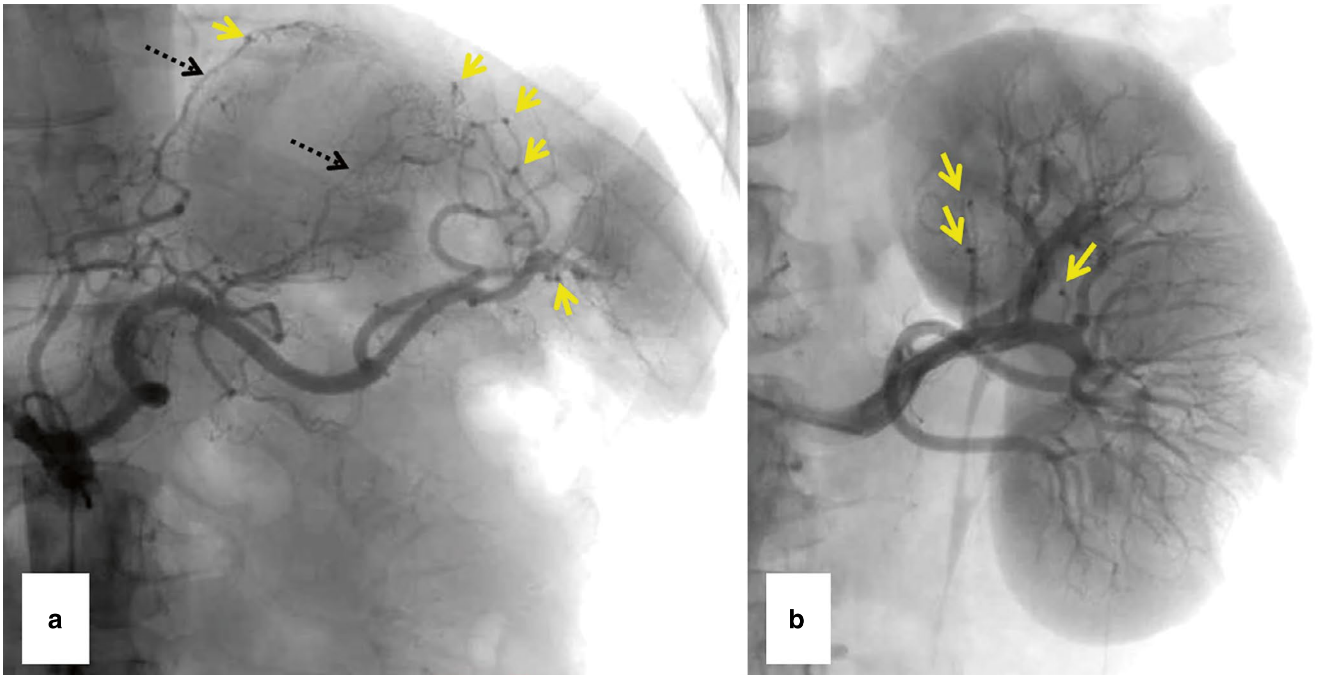

Fig. 16.2 Splanchnic and renal arteriography from a patient with polyarteritis nodosa. (**a**) Microaneurysms in the territory of the splenic artery (short arrows) and stenotic artery lesions in gastric arteries (dashed arrows). (**b**) Distal microaneurysms in the intrarenal arteries

Imaging Findings

Visceral angiography may be performed in situations in which PAN is highly suspected and histologic diagnosis of vasculitis cannot be achieved, or in patients predominantly experiencing symptoms suggestive of abdominal, renal, or cardiac involvement. In these situations, visceral angiography may have higher diagnostic yield than blinded muscle or peripheral nerve biopsies [12]. Arterial saccular or fusiform microaneurysms (1–5 mm in diameter) are the typical arteriographic lesions in PAN, and can coexist with stenotic lesions, predominantly in the renal, mesenteric, and celiac trunk artery branches (Fig. 16.2). Therefore, in the appropriate clinical context, the diagnosis of PAN can be established in the absence of histologic confirmation when characteristic angiographic changes are detected [3, 9, 12]. Apart from secondary causes of PAN-like necrotizing vasculitis, other conditions should be included in the differential diagnosis of multiple aneurysm formation, particularly structural vasculopathies [3].

Definition and Classification Criteria

The American College of Rheumatology (ACR) established classification criteria for PAN in 1990 including clinical, laboratory, angiographic, and histologic features [14]. These ACR criteria included HBV detection, but did not consider ANCA testing or MPA as a different condition from PAN. In the 1994 CHCC, PAN was defined as a primary (non-infectious) vasculitis different from MPA, a new entity considered a small-sized vessel vasculitis typically presenting with necrotizing glomerulonephritis and pulmonary capillaritis, and frequently associated with the presence of ANCA [2]. The negativity of ANCA in PAN was emphasized in the updated 2012 CHCC [1].

Before 1994 CHCC, the incidence of PAN had been overestimated [3, 9] and many patients previously diagnosed with PAN were later reclassified as having MPA or infection-related vasculitis. After 2012 CHCC, other secondary causes of vasculitis clinically and histologically indistinguishable from PAN were also placed in new categories, such as vasculitis associated with systemic disease (e.g., lupus or rheumatoid vasculitis), vasculitis associated with probable etiology (e.g., HBV-associated vasculitis or cancer-associated vasculitis), and single-organ vasculitis (SOV) (e.g., cutaneous arteritis, primary central nervous system vasculitis or focal vasculitis involving gallbladder, appendix and other organs or territories) [1, 6].

With regard to single-organ vasculitis, necrotizing vasculitis localized within a specific organ or territory with no apparent systemic involvement histologically resembling PAN have been repeatedly reported [6]. Focal vasculitis isolated to the appendix, intestines, gallbladder, pancreas, breast, male and female genital organs, and urinary structures is usually found incidentally in organs excised because of focal symptoms or cancer suspicion. They can be cured by resection of the involved tissues, and systemic treatment is

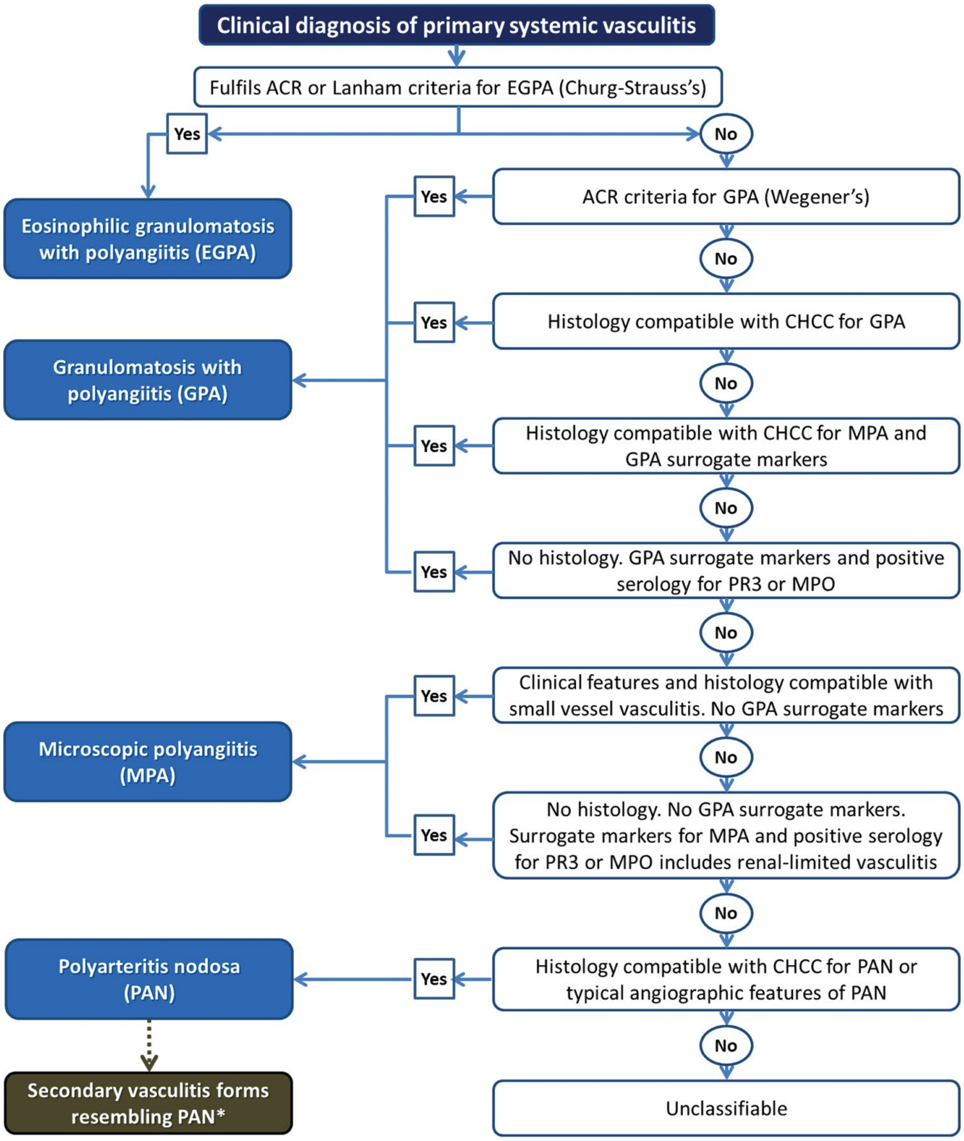
Clinical diagnosis of primary systemic vasculitis
Fulfils ACR or Lanham criteria for EGPA (Churg-Strauss's)
Yes
No
Eosinophilic granulomatosis with polyangiitis (EGPA)
Yes
ACR criteria for GPA (Wegener's)
No
Yes
Histology compatible with CHCC for GPA
Granulomatosis with polyangiitis (GPA)
No
Yes
Histology compatible with CHCC for MPA and GPA surrogate markers
No
Yes
No histology. GPA surrogate markers and positive serology for PR3 or MPO
No
Yes
Clinical features and histology compatible with small vessel vasculitis. No GPA surrogate markers
Microscopic polyangiitis (MPA)
No
Yes
No histology. No GPA surrogate markers. Surrogate markers for MPA and positive serology for PR3 or MPO includes renal-limited vasculitis
No
Polyarteritis nodosa (PAN)
Yes
Histology compatible with CHCC for PAN or typical angiographic features of PAN
No
Secondary vasculitis forms resembling PAN*
Unclassifiable

Fig. 16.3 European Medicine Agency consensus algorithm for the classification of eosinophilic granulomatosis with polyangiitis (EGPA), granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and polyarteritis nodosa (PAN). [Adapted and modified from ref [9]]. *Note*: The Lanham criteria for EGPA and the surrogate markers for GPA and MPA are explained in detail in reference [9]. * Secondary forms of vasculitis resembling PAN include vasculitis associated with systemic disease (e.g. lupus or rheumatoid vasculitis), vasculitis associated with probable etiology (e.g. HBV-associated vasculitis or cancer-associated vasculitis), and vasculitis associated with monogenic autoinflammatory diseases (e.g. DADA2 and VEXAS syndrome). ACR: American College of Rheumatology; CHCC: Chapel Hill Consensus Conference; DADA2: deficiency of adenosine deaminase 2; PR3: Proteinase 3; MPO: Myeloperoxidase; VEXAS: Vacuoles, E1 enzyme, X-linked, Auto-inflammatory, Somatic

not usually required. Because the terminology for these forms of localized vasculitis has been changed after 2012 CHCC, the term PAN (indicating a systemic process) is no longer recommended for single-organ vasculitis [6].

The European Medicine Agency consensus algorithm for the classification of PAN and other necrotizing vasculitides proposed by Watts et al. in 2007 combined ACR criteria and 1994 Chapel Hill definitions with ANCA testing and surrogate markers of vascular inflammation (Fig. 16.3) [9]. This classificatory scheme has repeatedly validated and definitively confirmed the low prevalence of PAN [3]. However, the establishment of secondary vasculitis as new categories in the 2012 CHCC and the recent advent of monogenic autoinflammatory diseases that may present with vasculitis affecting all vessel sizes, such as DADA2 and VEXAS syndrome, has made evolve this algorithm (Fig. 16.3), which now leaves PAN even more infrequent after ruling out these secondary causes of vasculitis. Although new diagnostic criteria have been proposed [15], the current classification criteria for PAN are not totally satisfactory and therefore international collaborative efforts to establish better diagnostic and classification criteria for PAN have been planned [3].

Disease Course and Prognosis

Contrarily to MPA and GPA, known for being multi-relapsing diseases, PAN has been classically considered a monophasic disease with a relapse rate lesser than 10%. However, in some studies, relapses have been described higher, similar to that described in patients with MPA [3]. In addition, a large PAN series recently reported relapses in 40% of patients [4].

The prognosis of PAN depends on the organs involved. The French Vasculitis Study Group (FVSG) proposed the Five Factor Score (FFS) in 1996, a prognosis index considering the following items: presence of severe gastrointestinal tract disease (defined as bleeding, perforation, infarction, or pancreatitis), serum creatinine ≥1.58 mg/dL and proteinuria (≥1 g/day) (both items for renal involvement), cardiac disease (infarction or heart failure), and central nervous system involvement. When present, each of those provided a score of 1 [16]. The 5-year mortality of PAN patients with FFS = 0 was 12%, for those with FFS = 1 was 26%, and in cases with FFS ≥2, mortality was 46%. The overall 7-year survival was 79% [16]. A 2011 updated version of FFS also included age >65 years and renal insufficiency (not considering proteinuria) as poor prognosis factors [17].

Treatment

The level of evidence supporting therapeutic decisions in PAN is low [18]. The existing randomized clinical trials have been performed on mixed cohorts of patients with PAN, EGPA, and MPA [16]. The extent of the involved organs and disease progression are the two principal determinants for treating patients with PAN. Mild forms of PAN (with FFS = 0) can be treated with glucocorticoids only, typically prednisone or prednisolone at doses of 1 mg/kg/day at least for 1 month, with subsequent tapering [3, 16]. When prednisone cannot be tapered below 15–20 mg/day because of active disease or relapse, the addition of a second immunosuppressive drug is recommended. In life-threatening situations or rapidly progressive disease, high doses of intravenous methylprednisolone (1000 mg/day for 3 days) are advised. When critical organs are involved (FFS ≥1), in addition to prednisone, cyclophosphamide is recommended at doses of 2 mg/kg/day orally or as monthly intravenous doses of 0.6 g/m^2 for 6–12 months [3]. Given the better safety profile, monthly intravenous pulses administration is preferred to daily oral cyclophosphamide, and treatment beyond 12 months is not advised. From the evidence obtained in clinical trials with MPA and GPA patients, cyclophosphamide is recommended to induce remission, which has to be maintained by switching it by a safer immunosuppressive agent such as azathioprine or methotrexate [3]. Angiographic abnormalities can regress after treatment [11]. Surgery or endovascular repair may be required for some disease complications, such as perforation/rupture, ischemia or hemorrhage of the gastrointestinal organs or kidneys [11].

The experience in treating patients with PAN refractory to conventional therapies with biologic agents is still limited. However, a European collaborative study found remission or partial response in 53%, 50%, and 44% of patients treated with anti-TNF agents, tocilizumab, and rituximab, respectively, with the highest remission rate (50%) obtained with tocilizumab. No effect was observed with the use of anakinra, alemtuzumab, interferon-alpha, and abatacept [19].

In patients with HBV-associated vasculitis, a combination of short glucocorticoid treatment with plasma exchanges and antiviral therapy (currently tenofovir or entecavir) may be effective to facilitate viral seroconversion and secondarily control disease activity. The control of the viremia is also useful in preventing the development of long-term HVB hepatic complications [3, 10]. Relapses are rare in HBV-vasculitis and never occur when viral replication has ceased and seroconversion has been achieved [11]. In other infections causing vasculitis, such as HIV-associated vasculitis, the same therapeutic approach (short glucocorticoid treatment followed by specific anti-viral therapy) has been reported effective [20]. In vasculitis associated with other diseases, such as malignancies or autoinflammatory diseases, apart from controlling local and systemic consequences of vascular inflammatory lesions with glucocorticoids, proper targeted treatments of the primary condition are always warranted.

Conclusions

PAN is a primary systemic necrotizing vasculitis that has become almost an ultra-rare condition after other primary and secondary systemic vasculitides clinically and histologically resembling PAN have been discovered over time. Current treatment options for PAN are still limited. Consequently, international efforts are still necessary to establish valid diagnostic and classification criteria for PAN, as well to improve its therapeutic strategies.

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17

Microscopic Polyangiitis

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Abstract

Microscopic polyangiitis (MPA) belongs to the antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (AAVs). MPA is clinically characterized by small-vessel vasculitis primarily affecting the kidneys and the lungs, but other organs may be involved as well. Renal involvement is clinically apparent as rapidly progressive glomerulonephritis and histopathologically as pauci-immune necrotizing and crescentic glomerulonephritis. ANCAs in MPA are mainly directed to myeloperoxidase (MPO-ANCA). The first formal classification criteria for MPA have been recently established. Induction treatment consists of cyclophosphamide or rituximab and glucocorticoids followed by maintenance therapy. A new targeted treatment, avacopan, has recently been approved.

Keywords

Microscopic polyangiitis · ANCA-associated vasculitis · Antineutrophil cytoplasmic autoantibodies · Antimyeloperoxidase antibodies · Myeloperoxidase · Necrotizing and crescentic glomerulonephritis

Definition

Microscopic polyangiitis (MPA) was defined by the Revised International Chapel Hill Consensus Conference (CHCC) [1] as "necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels. Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Inflammation that is not centered on vessels, including granulomatous inflammation, is absent." Antineutrophil cytoplasmic autoantibodies (ANCAs) are present in most of the cases and are, in a majority of patients, directed against myeloperoxidase (MPO-ANCA).

According to the Chapel Hill Consensus Conference, the disease belongs to the ANCA-associated vasculitides (AAVs).

Epidemiology

The AAVs, mainly comprising of granulomatosis with polyangiitis (GPA) and MPA, have been estimated to have an overall incidence of 13–21 per million [2]. Unlike GPA, the incidence of MPA is higher in southern Europe than in northern Europe [3]. The mean pooled incidence rate for MPA has increased over the last two decades. Possible explanations would be, in part, a higher availability of ANCA testing, the evolution of classification criteria as well as increased aware-

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ness of physicians. The average age of onset is between 60 and 65 years. Female predominance has been reported in the majority of studies [2].

Pathogenesis

Loss of tolerance leads to the development of ANCAs, autoantibodies that activate neutrophils [4]. Strong evidence exists that MPO-ANCAs are directly involved in the pathogenesis of MPA. The vast majority of patients with MPA (95%) are positive for ANCA, directed to MPO in 70% of cases and directed to proteinase 3 (PR3) in the remaining patients. There is also a close relationship between plasma levels of autoantibodies and clinical activity of vasculitis [5]. ANCA-activated neutrophils induce microvascular inflammation and endothelial damage and release the autoantigen for presentation by antigen-presenting cells, allowing antigen recognition by effector T cells, which mediate further injury [4]. The most convincing argument for a pathogenic role of MPO-ANCA comes from studies in experimental animals. Xiao et al. [6] immunized MPO-deficient mice with mouse MPO resulting in the production of antimouse MPO antibodies. Splenocytes from these mice were injected into immunodeficient and normal mice, which resulted in the development of severe necrotizing and crescentic glomerulonephritis and systemic necrotizing vasculitis including pulmonary capillaritis. Immune deposits were hardly present, consistent with so-called pauci-immune vasculitis and glomerulonephritis, which are seen also in patients with MPA.

Besides direct activation of neutrophils, anti-MPO antibodies may participate in the inflammatory process by several other ways: enhancing the peroxidase activity of MPO, and inducing formation of neutrophil extracellular traps (NETs), creating a vicious cycle as abnormal formation of NETs has been associated with the triggering of the autoimmune response against neutrophil components [7].

The mechanisms underlying the production of ANCA are still elusive. The genome-wide association study (GWAS) has shown that AAV with anti-MPO antibodies is associated with HLA-DQ polymorphisms [8]. Environmental factors, such as silica exposure, pesticides, fertilizer exposure, solvents, or carbon monoxide levels, among others, may play a role in the development of autoimmunity in AAV [4].

Clinical Manifestations

MPA belongs to the systemic vasculitides indicating that multiple organs can be affected. Major organs involved in MPA are the kidneys and the lungs. Renal involvement is manifested by microscopic hematuria with cellular casts in combination with proteinuria, which is, generally, not massive. In addition, deterioration of renal function frequently occurs clinically apparent as rapidly progressive glomerulonephritis. In close to 75% of patients the kidneys are involved, 10% end up with renal replacement therapy, and 20% of patients die [9].

MPA can be restricted to the kidneys. This ANCA-associated condition, in the majority of cases MPO-ANCA-associated, is designated as idiopathic necrotizing and crescentic glomerulonephritis. Renal-limited vasculitis is treated according to the guidelines for the treatment of MPA.

Lung involvement occurs somewhat less frequently and is clinically apparent as dyspnea, cough, and hemoptysis (not in all cases). The chest X-ray may show an alveolar filling pattern. Pulmonary hemorrhage is a very serious condition with bad prognosis, particularly in those patients who also have rapidly progressive glomerulonephritis (so-called renal–pulmonary syndrome). As mentioned, many organs may be affected. Besides general malaise, weight loss, and fever, arthralgia/myalgia, skin involvement such as purpura, and, particularly, involvement of peripheral nerves (mononeuritis multiplex) are frequent findings.

In contrast to GPA, granulomatous inflammation with local tissue destruction is generally absent in MPA, and ENT abnormalities such as recurrent sinusitis, bloody nasal discharge, and cartilage destruction leading to saddle nose deformity are not characteristic for MPA. Table 17.1 summarizes the main clinical features of MPA [9–13].

Table 17.1 Microscopic polyangiitis: clinical features and organ or system involvement, expressed as percentages of the studied population

	Nguyen et al. [9]	Schirmer et al. [10]	Hogan et al. [11]	Shi et al. [12]	Furuta et al.[a] [13]	Furuta et al.[a] [13]
Number of patients	378	144	107	124	147	312
General	40.2–45.2%	91.7%	–	54.8%	84.4%	75.0%
Lung manifestations	40.2%	50.0%	36.0%	61.3%	34.7%	52.5%
Alveolar hemorrhage	15.6%	22.2%	–	16.1%	20.4%	10.6%
Renal manifestations	74.3%	79.2%	100.0%	100.0%	82.3%	86.9%
Cutaneous manifestations	41.0%	16.7%	12.0%	6.5%	24.5%	11.2%
Ear, nose, and throat manifestations	13.2%	2.1%	13.0%	0.8%	13.6%	12.2%
Eye involvement	4.8%	10.4%	2.0%	1.6%	15.0%	6.7%
Cardiovascular manifestations	20.9%	6.3%	–	12.1%	4.1%	2.9%
Gastrointestinal manifestations	16.4%	3.5%	8.0%	2.4%	2.7%	4.2%
Neurological manifestations	50.5%	38.9%	8.0%	16.9%	19.7%	29.5%

[a] This manuscript details the clinical characteristics of different cohorts. All of them are displayed in this table

Pathological Features

MPA is part of the AAVs that are characterized by necrotizing vasculitis of small vessels (arterioles, capillaries, venules) and lack or paucity of immune deposits within the vessel wall. In the skin, this is apparent as leukocytoclastic vasculitis. Capillaritis with fibrinoid necrosis is the typical finding in the lungs in MPA. Granulomatous inflammation is a characteristic finding in (PR3-ANCA-associated) GPA but not in (MPO-ANCA-associated) MPA. The renal lesions are designated as necrotizing crescentic glomerulonephritis. Focal thrombosis of glomerular capillaries with fibrinoid necrosis is an early lesion that is followed by rupture of the glomerular basement membrane and extracapillary proliferation. This results in crescent formation, initially cellular crescents and later on more fibrous crescents. Periglomerular accumulation of mononuclear cells follows the glomerular inflammatory process. Deposition of immunoglobulins and complement is hardly seen (pauci-immune glomerulonephritis) (Fig. 17.1).

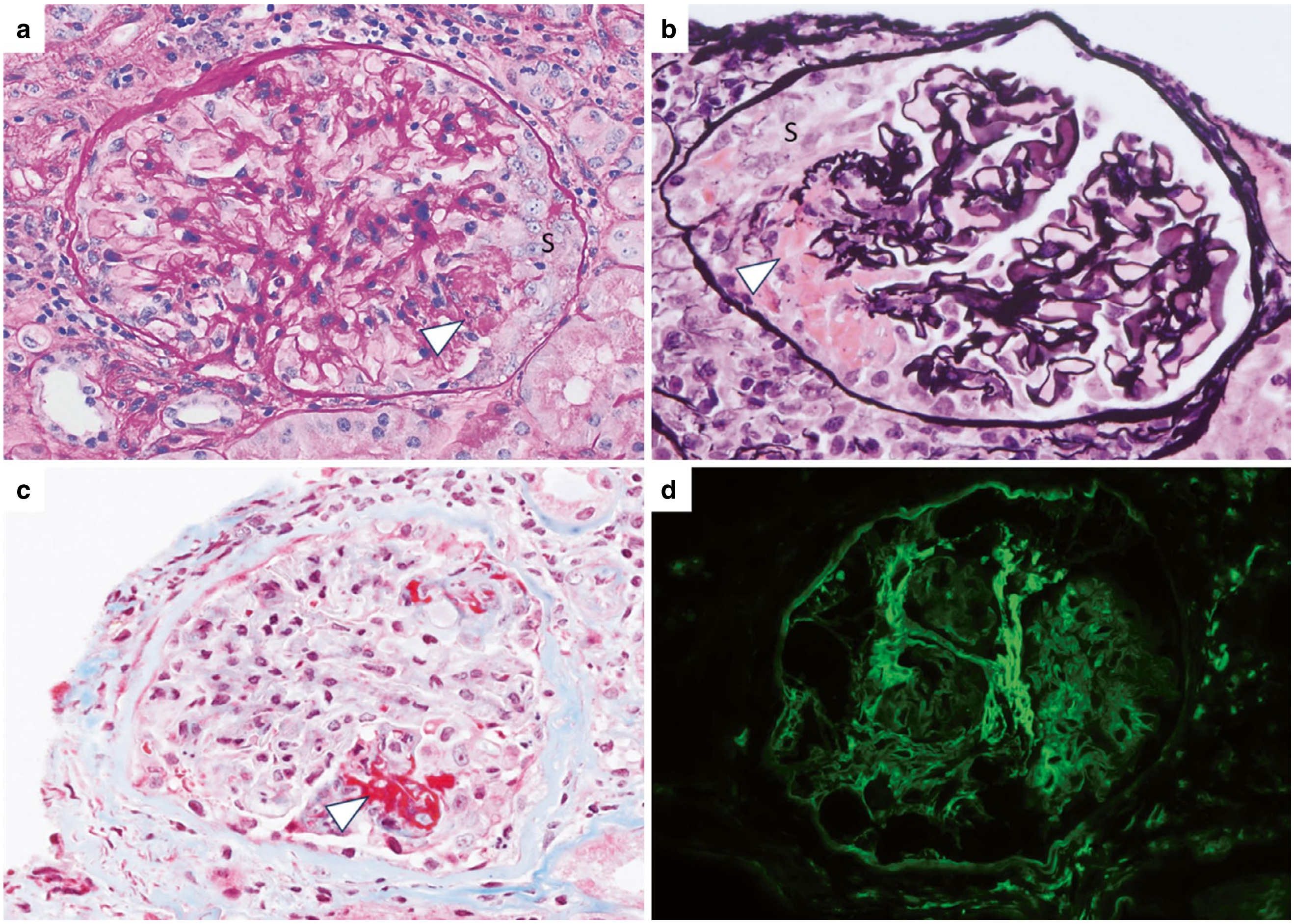

Fig. 17.1 Active glomerular lesions associated with microscopic polyangiitis: presence of segmental fibrinoid necrosis (**a**–**c**, areas indicated with arrowhead), which generates disruption of the capillary wall (better identified in panel **b**) and extracapillary proliferation with the formation of cellular crescents (**a**, **b** areas marked "S"). Direct immunofluorescence (IFD) study, positivity for fibrinogen was observed (**d**). [Stains: (**a**) PAS, (**b**) Silver, (**c**) Trichrome, (**d**) Fibrinogen (IFD) 400×]

Serological Features

As MPA belongs to the AAVs, ANCAs are the diagnostic hallmark of MPA. Ninety percent of patients with MPA are positive for ANCAs, the majority of whom (70%) being positive for MPO-ANCAs. ANCAs are routinely assessed by indirect immunofluorescence on ethanol-fixed neutrophils. A classic cytoplasmic staining pattern with accentuation of the fluorescence within the nuclear lobes is characteristic for PR3-ANCAs, whereas MPO-ANCAs produce a perinuclear staining pattern. Such a perinuclear pattern is, however, far from specific for MPO-ANCA and may be produced as well by ANCA directed to other neutrophil antigens such as lactoferrin which are not specific for AAVs. Therefore, a positive test for ANCA should always be followed by an antigen-specific test, usually ELISA with specificity for PR3-ANCA and MPO-ANCA. Besides ANCAs, rheumatoid factor and anti-endothelial cell antibodies are frequently present in MPA. They lack, however, specificity for this disease. Table 17.2 summarizes the main laboratory findings and serological markers of MPA [9, 12, 13].

Table 17.2 Microscopic polyangiitis: laboratory findings and serological markers of active disease, expressed as median (IQR)[a] or median (range)[b]

	Nguyen et al. [9][a]	Shi et al. [12][a]	Furuta et al. [13][b]	Furuta et al.* [13][b]	Furuta et al.* [13][b]	Furuta et al.* [13][b]
Number of patients	378	124	147	312	254	48
Creatinine, µmol/L	130 (80–265)	353.0 (133.8–582.5)	221.9 (58.3–1882.9)	159.1 (26.5–2130.4)	335.0 (54.8–1670.8)	108.7 (35.4–998.9)
CRP, mg/L	–	71.5 (21.7–98.9)	72.0 (1.0–350.0)	62.7 (0.2–383.1)	41.0 (0.3–552.0)	65.3 (0.5–313)
MPO/p-ANCA positive	95.9%	94.4%	69.4%	95.8%	69.8%	100%
PR3/c-ANCA positive	3.1%	5.6%	22.4%	3.2%	27.8%	0%
ANCA negative	13.9%	0%	10.2%	3.5%	4.0%	0%

* This manuscript details the laboratory findings and serological markers of different cohorts. All of them are displayed in this table

Diagnostic Criteria

Whereas polyarteritis nodosa (PAN) was described already in 1866 by Kussmaul and Maier, microscopic polyarteritis was suggested in 1985 as a disease entity by Savage et al. [14]. It was described as a disease in which rapidly progressive glomerulonephritis, not infrequently in conjunction with pulmonary capillaritis, was a prominent finding. MPA was not recognized as a separate entity in the 1990 American College of Rheumatology (ACR) classification criteria for vasculitis, but the disease was defined by the CHCC [15]. Originally published in 1994, and then revised in 2012 [1], the CHCC provided the definitions of distinct classes of vasculitis to establish the structure for a classification system (Table 17.3). This definition describes MPA as “necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small- and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.”

In the literature, most authors have used this definition to classify patients as having MPA. It is clear from the definition that histopathological evidence of pauci-immune necrotizing small-vessel vasculitis is necessary to make a diagnosis of MPA. The European Medicines Agency (EMA) algorithm was developed to classify ANCA vasculitides and PAN for epidemiological studies [16] but does not represent a classification system. Very recently, the 2022 ACR/EULAR (European Alliance of Associations for Rheumatology) MPA classification criteria have been published [17] (Table 17.3). These are the first formal criteria for MPA. Using data from the multinational prospective DCVAS study, a 5-stage approach has been used to establish the criteria with an expert review and consensus at each stage. The comparator group for developing and validating the criteria were predominantly patients with other forms of AAV and other small- and medium-vessel vasculitides. The new criteria for MPA have a sensitivity of 91% (95% CI 85–95%) and the specificity was 94% (95% CI 92–96%) in the validation data set and as a novelty, incorporate ANCA testing. These criteria are intended for the purpose of classification of vasculitis in research settings and are not appropriate for use in establishing a diagnosis of vasculitis. Therefore, the criteria should only be applied when a diagnosis of small- or medium-vessel vasculitis has been made and all potential “vasculitis mimics” have been excluded.

Table 17.3 Nomenclature and classification criteria for microscopic polyangiitis

Chapel Hill consensus conference nomenclature (2012) [1]	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small- and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs	Nomenclature system
American College of Rheumatology/ European Alliance of Associations for Rheumatology (2022) [16]	*Clinical criteria*	A patient can only be classified as MPA if two requirements are fulfilled: (1) an established diagnosis of small- or medium-vessel vasculitis and (2) the exclusion of vasculitis mimics
	Nasal involvement: bloody discharge, ulcers, crusting, congestion blockade, or septal defect/perforation (**−3**)	
	Laboratory, imaging, and biopsy criteria	
	Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies ANCA positive **(+6)**	
	Fibrosis or interstitial lung disease on chest imaging (**+3**)	Sum the scores for 6 items, a score ≥5 is needed for classification of MPA
	Pauciimmune glomerulonephritis on biopsy (**+3**)	
	Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies ANCA positive (**−1**)	Sensitivity of 91% and a specificity of 94%
	Blood eosinophil count ≥1000/μL (**−4**)	

Treatment

Induction treatment consists of either cyclophosphamide or rituximab and high-dose glucocorticoids (GC). Rituximab was not inferior to intravenous cyclophosphamide in two high-quality clinical trials. The current guidelines recommend reduced GC tapering regimens and lower starting prednisone doses. In patients presenting with a serum creatinine value of >300 μmol/L, the additional use of plasma exchange might be considered. Avacopan is a C5a receptor inhibitor recently approved as adjunctive GC-substitute/sparing agent [18, 19]. Once remission has been obtained, maintenance treatment is advocated for another 24–48 months. Rituximab is preferred for maintenance treatment and azathioprine or methotrexate may be considered as an alternative [18].

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Granulomatosis with Polyangiitis

18

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Abstract

Granulomatosis with polyangiitis (GPA), a rare systemic autoimmune disease associated with antineutrophil cytoplasmic antibodies (ANCA), is a small vessel necrotizing vasculitis characterized by granulomatous inflammatory lesions. Presentation ranges from mild to severe clinical disease, due to necrotizing granulomatous involvement of the upper and lower respiratory tract and vasculitis, primarily affecting the lung, kidneys, peripheral nerves, and skin. The diagnosis of GPA is based upon the combination of characteristic clinical findings, laboratory and imaging results, ANCA positivity (mainly directed against proteinase-3), and histopathology features. New classification criteria endorsed by the American College of Rheumatology and the European Alliance of Associations for Rheumatology have been recently developed. Initial treatment of organ- or life-threatening GPA relies on the administration of rituximab or cyclophosphamide and glucocorticoids, which are then switched to less potent immunosuppressive therapies for maintenance of remission. Unfortunately, GPA may be associated with increased morbidity and mortality.

Keywords

ANCA · Vasculitis · Granulomatosis with polyangiitis · Proteinase-3

Definition

Granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis) is a primary, autoimmune disease characterized by necrotizing granulomatous inflammatory lesions and vasculitis, mostly involving the upper airway and lower respiratory tract, often associated with pauci-immune glomerulonephritis [1]. GPA is part of the antineutrophil cytoplasmic antibodies (ANCA) vasculitis, a group of rare, multisystemic vasculitides that predominantly affects small-sized blood vessels (i.e., capillaries, venules, arterioles, and small arteries), in presence of ANCA specific for proteinase-3 (PR3) or myeloperoxidase (MPO) [1].

Epidemiology

GPA is an uncommon disease, with a prevalence of 2.3–146 cases/million and annual incidence of 2–13 cases/million person-years [2]. The disease has a north-south gradient and is diagnosed predominantly in white populations of Northern Europe but is rarely observed in China and Japan. Age at onset ranges between 45 and 65 years, with men and women being equally affected [2].

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Physiopathology

Environmental and genetic factors. The precise etiology of GPA is unknown, although multiple environmental and genetic factors may play a relevant role. Infectious agents (e.g., *Staphylococcus aureus* and Ross River virus), environmental precipitants (farming, exposure to mercury, lead, pesticides, and silica), and certain drugs (e.g., hydralazine, propylthiouracil, and cocaine) have been postulated as possible triggers for GPA development [3, 4]. In addition, variants in genes such as HLA-DPB1, PTPN22, SERPINA1, and PRTN3 (gene encoding for PR3) confer higher susceptibility to GPA.

Pathogenetic mechanisms. Clinical evidence and in vitro and animal experimental data indicate that ANCA are pathogenic. The leading theory of the pathogenesis of ANCA-induced vascular inflammation proposes that this complex multifactorial autoimmune process begins with the development of ANCA in predisposed individuals. Once ANCA have emerged, interaction of these autoantibodies with PR3 and MPO at the surface of neutrophils (and monocytes) leads to full cellular activation with generation of lysosomal proteolytic enzymes, proinflammatory cytokines, oxygen radicals, extrusion of neutrophil extracellular traps, and activation of the alternative complement pathway, which results in damage, injury, and necrosis of organ tissue [3, 4]. In addition to vasculitis, GPA is also characterized by the presence of necrotizing granulomatous inflammation. It has been hypothesized that GPA granulomatosis may be initiated by the activation of neutrophils located in the extravascular compartment by ANCA, in a process similar to that described for vascular inflammation [3, 4]. The intense damage, tissue necrosis, and inflammation then would engender an exaggerated innate inflammatory response attracting a high influx of mononuclear cells. Over time, lesions with increasing number of monocytes evolve toward more typical granulomas, with formation of giant cells, macrophages (walling off the necrotic debris), dendritic cells, B- and T-lymphocytes, eosinophils, and plasma cells [3, 4]. An alternative theory suggests that PR3 interacts with dendritic cells and induces their maturation into antigen-presenting cells, which are able to prime T-cells for a Th1-phenotype, thus leading to an autoantigen-driven process that results in granuloma formation and ANCA production.

Pathology. GPA histopathology cardinal features include granulomatous inflammation, necrosis, and vasculitis [1]. Necrotizing granulomatous lesions in the upper and lower respiratory tract are accompanied by necrotizing vasculitis of small arteries and veins [4]. Pauci-immune focal and segmental, necrotizing, crescentic glomerulonephritis (NCGN) is a typical finding (Fig. 18.1) [4].

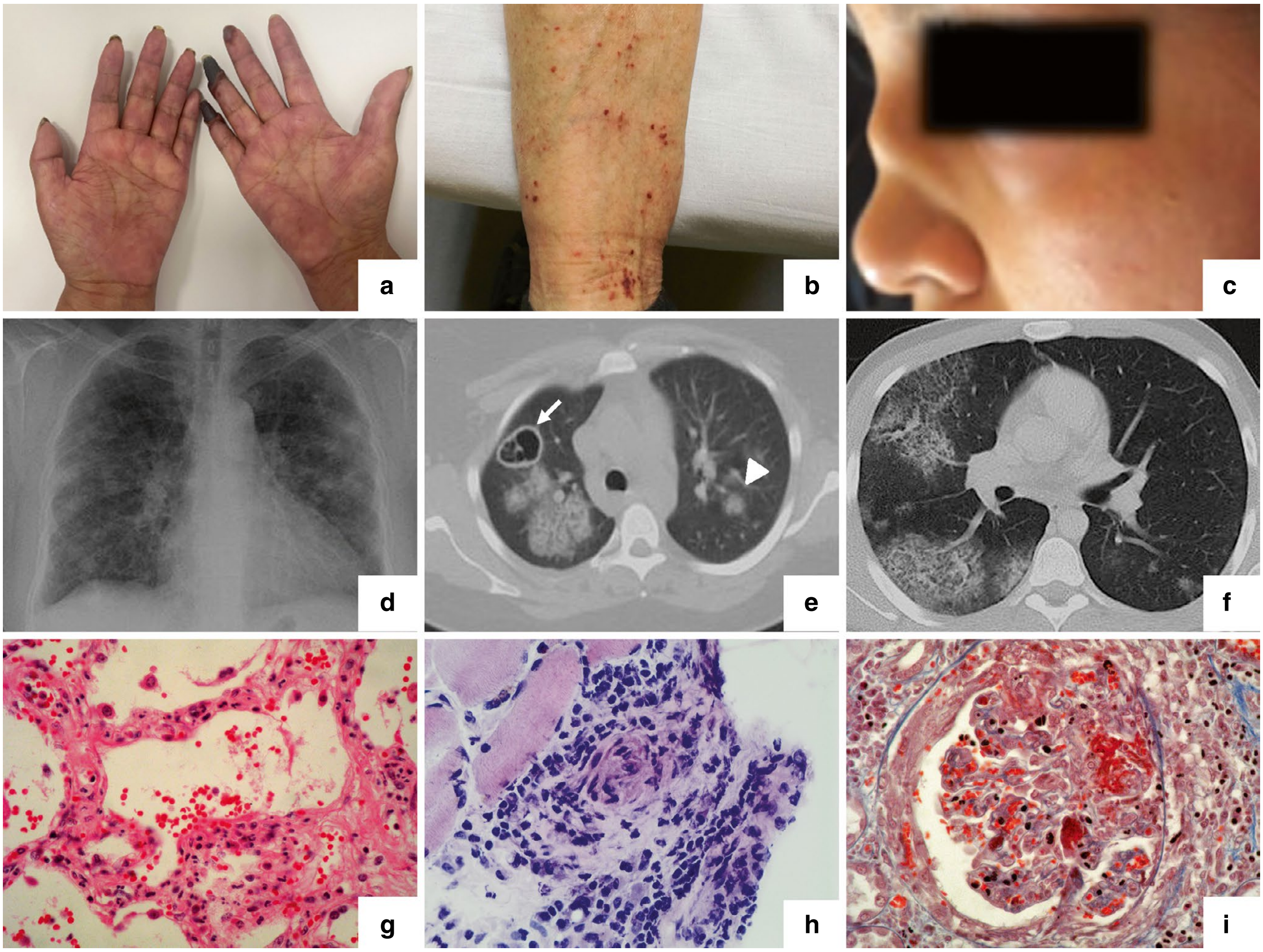

Fig. 18.1 Clinical, radiological, and pathology features of granulomatosis with polyangiitis. (**a**) Digital necrosis. (Courtesy of Dr. Violeta Higuera Ortiz). (**b**) Palpable purpura, typically involving lower extremities. (Courtesy of Dr. Sara Beça). (**c**) Nasal deformity with a saddle-nose appearance, a frequent granulomatous complication. (Courtesy of Dr. Natyelli Ruiz). (**d**) Chest radiograph of a PR3-ANCA GPA patient showing multiple nodular parenchymal opacities. (**e**) Chest computed tomography (CT) demonstrating multiple pulmonary nodules (arrowhead), an irregular thick-walled cavitated mass (arrow), and extensive areas of ground glass opacities. (**f**) Alveolar hemorrhage evidenced in pulmonary CT as extensive, patchy ground glass opacities. (**g**) Neutrophilic capillaritis demonstrated in the autopsy of a patient with pulmonary-renal syndrome. (**h**) Muscle biopsy showing necrotizing, fibrinoid, small vessel vasculitis. The inflammatory infiltrate is predominantly composed by neutrophils. (**i**) Light micrograph showing segmental necrotizing glomerulonephritis

Clinical Manifestations

GPA can involve the small blood vessels of virtually any organ or tissue. Therefore, clinical manifestations are heterogeneous, and presentation varies from mild to life-threatening disease. The spectrum of GPA is sustained by vasculitic symptoms (e.g., pulmonary hemorrhage, NCGN, mononeuritis multiplex) and granulomatous manifestations (e.g., orbital masses, pulmonary nodules, pachymeningitis) (Table 18.1). Most patients present with constitutional symptoms as well as musculoskeletal involvement such as arthralgia and myalgia [5–8]. Ear, nose, and throat (ENT) manifestations, a predominant feature of GPA, include nasal bloody/purulent discharge, crusting, nasal ulcers, persistent rhinorrhea, anosmia, chronic sinusitis, subglottic stenosis, perforation of the nasal septum and saddle nose deformity, chronic otitis media, otorrhea, mastoiditis, conductive and sensorineural hearing loss, oral ulcers, palate necrosis, and strawberry gingivitis (Fig. 18.1) [5–8].

Pulmonary disease, another outstanding characteristic of GPA, may be presented as cough, dyspnea, chest pain, pleuritis, alveolar hemorrhage, lung nodules, masses, cavitations, and bronchial stenosis (Fig. 18.1) [5–11]. Kidney involvement may be associated with hematuria, proteinuria, and active urine sediment. It may be slowly progressive or fulminant, presenting as rapidly progressive glomerulonephritis that may progress to end-stage kidney disease (ESKD) within days to weeks [5–8]. Cutaneous manifestations include palpable purpura, subcutaneous nodules, papules, urticaria, ulcers, or digital necrosis, whereas neurologic involvement typically presents as mononeuritis multiplex or sensorimotor neuropathy (Fig. 18.1) [5–8]. Central nervous system disease (e.g., cranial neuropathy, hypertrophic pachymeningitis, pituitary gland involvement) is rare. Within the eye, GPA active disease features include conjunctivitis, episcleritis, scleritis, dacryocystitis, and rarely necrotizing keratitis, optic neuritis, uveitis, or retroorbital masses. Uncommon manifestations include pericarditis, granulomatous myocarditis, mesenteric ischemia, and gut infarction and perforation [5–8]. The incidence of venous thromboembolism is increased in active GPA disease.

Table 18.1 Frequency of organ manifestations

	At presentation	During disease course
Systemic manifestations		
Fever	23–43%	50%
Weight loss	15–44%	50%
Fatigue	60%	
Arthralgia/arthritis	20–61%	67–84%
Ear, nose, throat	73–93%	75–99%
Sinusitis	40–51%	68–85%
Rhinitis	53%	
Nasal crust	38%	
Epistaxis	20%	
Saddle nose	1.3%	
Subglottic stenosis	2–8%	16%
Oral lesions (ulcers, gingivitis)	3%	10%
Otitis media	25%	44%
Hearing loss	14%	42%
Lung	55–68%	62–90%
Cough	19%	46%
Infiltrates	18–23%	66%
Nodules	22–41%	59%
Alveolar hemorrhage	18%	
Kidney	18–60%	38–72%
Skin	13–25%	25–46%
Palpable purpura	16%	
Eye	15–40%	52–61%
Conjunctivitis	5%	18%
Dacryocystitis	1%	18%
Scleritis	4–6%	16%
Episcleritis	9%	
Proptosis	2–4%	15%
Nervous system	24%	
Peripheral nervous system	21%	15–40%
Central nervous system	3–6%	11–15%
Heart	6–13%	15–25%
Gastrointestinal tract	1–5%	6–10%

Data derived from cohorts including >150 patients with granulomatosis with polyangiitis [5–8]

Laboratory Test and Radiologic Findings

Patients with active systemic GPA often show an intense inflammatory response. Table 18.2 summarizes the main laboratory results and computed tomography (CT) findings of GPA.

Table 18.2 Laboratory and image features at diagnosis in granulomatosis with polyangiitis

Laboratory findings [5–8]		Pulmonary computed tomography features [8–11]	
	Characteristic		Percentage
Anemia, normochromic/normocytic	29–70% (mean 11.1 g/dL)	Ground glass opacities	24–42%
Leukocytosis	33% (mean 10.5–11.4/μL)	Consolidations	26%
Thrombocytosis	65% (mean 481,000/μL)	Nodules (multiple, bilateral)	40–70%
Eosinophilia	Mild elevation	Unspecific lung infiltrates	19%
Erythrocyte sedimentation rate	70–80% (mean 71–84 mm/h)	Masses	32–60%
C-reactive protein	Usually highly elevated	Cavitations	30–50%
Elevated creatinine	29–43% (mean 2–3.3 mg/dL)	Segmental bronchial wall thickening	50%
Hematuria	38–46%	Bronchiectasis	19%
Proteinuria	35–47%	Hilar/mediastinal lymphadenopathy	2–14%
Red cell casts	35%	Pleural effusion	Rare
		Other findings in extra-pulmonary involvement may include chronic hypertrophic pachymeningitis, mastoiditis, opacification of paranasal sinuses and bone erosions, orbital masses, and tracheal stenosis	
Clinical indications for ANCA testing [12]			
Rapidly progressive glomerulonephritis			
Alveolar hemorrhage			
Pulmonary renal syndrome			
Cutaneous vasculitis with systemic features			
Multiple pulmonary nodules, after exclusion of infections and cancer			
Chronic destructive disease of the upper airways			
Long-standing sinusitis or otitis			
Subglottic tracheal stenoses			
Mononeuritis multiplex and sensitive motor peripheral neuropathy			
Retro-orbital mass			
Scleritis			

Note: ANCA detected by indirect immunofluorescence (especially p-ANCA) may be observed in inflammatory and infectious diseases, such as systemic lupus erythematosus, systemic sclerosis, ulcerative colitis, autoimmune hepatitis type 1, primary biliary cholangitis, tuberculosis, or infective endocarditis [13]

Serological Markers (ANCA Detection)

Standard methods for ANCA detection include indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assays (ELISA). By IIF staining, cytoplasmic (c-ANCA) and perinuclear (p-ANCA) patterns are identified, whereas ANCA target antigens PR3 and MPO are detected by ELISA [12, 13]. High-quality solid-phase immunoassays should be used for the primary screening of ANCA in patients with suggestive patterns of a small vessel vasculitis (Table 18.2). ANCA directed against PR3 (c-ANCA) or MPO (p-ANCA) are present in 65–90% and 20–30% of generalized GPA forms, respectively [12, 13]. Thus, PR3-ANCA have a high diagnostic value for GPA (sensitivity of 80% and specificity of 93%), although ANCA may be negative in 30–50% of patients with limited ENT involvement [12, 13].

Diagnosis

The diagnosis of GPA relies on a combination of characteristic clinical findings, compatible imaging study results, positive laboratory test results, supportive serologic markers, and histopathologic confirmation [2]. Basic laboratory workup should include complete blood count, serum creatinine and electrolytes levels, liver function test, urinalysis with urinary sediment, acute phase reactants, complement levels, anti-nuclear and anti-glomerular basement membrane (GBM) antibodies, cryoglobulins, serologies for HCV, HBV, HIV, and tuberculosis screening. Additional tests may include CT images of the lung and sinuses, nerve-conduction studies, pulmonary function tests and bronchoscopy, and ophthalmology examination. Histologic demonstration of characteristic features in affected organs (e.g., lung, kidney, skin, muscle, and peripheral nerves) remains the most definitive method to establish the diagnosis.

Diagnostic Criteria

No *diagnostic* criteria exist for diagnosing GPA or other ANCA vasculitides. However, several sets of *classification* criteria have been proposed to standardize the inclusion of GPA patients with uniform characteristics into clinical trials and epidemiological studies (Table 18.3).

American College of Rheumatology (ACR). In 1990, the ACR proposed the first formal set of criteria for the classification of GPA and six other vasculitides [14]. Their sensitivity and specificity for classification of GPA was 88.2% and 92%, respectively. *Strengths*. This was the first effort to develop a framework for international research activities in systemic vasculitis using a validated classification and were widely used. *Limitations*. ACR criteria were developed only to distinguish patients with GPA from other vasculitides and not from non-vasculitic conditions. Currently, these criteria do not perform well in modern cohorts because they were developed before the recognition of microscopic polyangiitis (MPA) as an independent phenotype of ANCA vasculitis and prior to the introduction of the widespread use of ANCA testing and modern vascular imaging techniques. Several studies have shown that they lack sufficient sensitivity and specificity to be used for diagnostic purposes in clinical practice.

Chapel Hill Consensus Conference (CHCC) nomenclature. Originally published in 1994, and then revised in 2012, the CHCC provided the definitions of distinct classes of vasculitis to establish the structure for a classification system [1]. *Strengths*. CHCC nomenclature has highly facilitated research on cohorts of patients with vasculitis. It established the most accepted standardized name and definition of GPA, as well as the most widely used division of vasculitis, that is, according to etiopathogenesis and predominant size of affected vessels. *Limitations*. The CHCC does not provide validated classification or diagnostic criteria for individual patients.

European Medicines Agency (EMA) algorithm. This stepwise hierarchical approach was developed to classify ANCA vasculitides and polyarteritis nodosa (PAN) for epidemiological studies [15]. GPA is classified when granulomatous inflammation is demonstrated by pathology or when GPA surrogate markers (e.g., pulmonary nodules, nasal crusting, subglottic stenosis) are associated with histological proof of vasculitis or ANCA positivity. *Strengths*. EMA algorithm provided a harmonized system for the classification of

Table 18.3 Nomenclature and classification criteria for granulomatosis with polyangiitis

American College of Rheumatology (1990) [14]	Nasal or oral inflammation	Presence of at least 2 of 4 criteria: sensitivity 88.2% and specificity 92.0%
	Abnormal chest radiography showing nodules, fixed pulmonary infiltrates, or cavities	
	Nephritic urinary sediment with hematuria or red cell casts	
	Granulomatous inflammation in biopsy. Histological granulomas within an artery or in the perivascular area of an artery or arteriole	
Chapel Hill Consensus Conference nomenclature (2012) [1]	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries, and veins). Necrotizing glomerulonephritis is common. Ocular vasculitis and pulmonary capillaritis with hemorrhage are frequent. Granulomatous and non-granulomatous extravascular inflammation are common	Nomenclature system
American College of Rheumatology/European Alliance of Associations for Rheumatology (2022) [16]	*Clinical criteria*	A patient can only be classified as GPA if two requirements are fulfilled: (1) an established diagnosis of small- or medium-vessel vasculitis and (2) the exclusion of vasculitis mimics
	Nasal involvement: bloody discharge, ulcers, crusting, congestion blockade, or septal defect/perforation (**+3**)	
	Cartilaginous involvement: inflammation on ear or nose cartilage, hoarse voice or stridor, endobronchial involvement, saddle nose deformity (**+2**)	
	Conductive or sensorineural hearing loss (**+1**)	
	Laboratory, imaging, and biopsy criteria	
	PR3-ANCA or cytoplasmic ANCA (**+5**)	
	Pulmonary nodules, mass, cavitation on chest imaging (**+2**)	Sum the scores for 10 items, a score ≥5 is needed for classification of GPA
	Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy (**+2**)	
	Inflammation, consolidation, or effusion of the nasal/paranasal sinuses, or mastoiditis on imaging (**+1**)	
	Pauci-immune glomerulonephritis on biopsy (**+1**)	Sensitivity of 92.5% (95% CI 86.9–96.2%) and a specificity of 93.8% (95% CI 88.9–97.0%)
	MPO-ANCA or perinuclear ANCA (**−1**)	
	Blood eosinophil count ≥1000/μL (**−4**)	

ANCA vasculitis and PAN by combining CHCC definitions, 1990 ACR classification criteria, and Lanham criteria for eosinophilic GPA (EGPA). In addition, it has been validated in several studies and has been reasonably successful at classifying patients into a single class. *Limitations.* The EMA system does not represent an original classification system and more importantly, in some studies, it overrepresents the classification of GPA patients.

American College of Rheumatology/European Alliance of Associations for Rheumatology (EULAR). The 2022 new classification criteria of GPA, endorsed by ACR/EULAR, were developed to be used in clinical research to distinguish GPA from MPA, EGPA, other forms of vasculitis, and other conditions mimicking vasculitis. The criteria consist of ten weighted clinical, laboratory, imaging, and pathologic parameters that combine to derive a risk score in patients with a diagnosis of small- or medium-vessel vasculitis when other medical conditions have been excluded [16]. Importantly, included characteristics are weighted to reflect the relative importance of specific items that help to discriminate between ANCA vasculitides (e.g., ANCA specificity is a major discriminator between GPA and MPA, while eosinophilia is a strong discriminator for EGPA). The sensitivity and specificity of ACR/EULAR GPA classification criteria was 92.5% and 93.8%, respectively [16]. *Strengths.* The new criteria reflect current standard of care by including ANCA and modern imaging and laboratory techniques, and therefore they outperformed the original ACR classification criteria for GPA with regard to sensitivity and specificity [16]. Additional improvements of the ACR/EULAR criteria include a novel methodology of data-driven approach, the use of the largest global cohort of patients (~7000 cases) ever assembled in vasculitis, the inclusion of controls, the incorporation of expert review for diagnostic reference, and its validation in an additional international cohort [17, 18]. *Limitations*. The relative weight of some criteria might need further discussion. For example, the item of PR3-ANCA detection (+5) outweighed by far other classical characteristics of GPA, such as the identification of granulomatous inflammation in tissue biopsies (+2) or clinical symptoms of cartilaginous involvement (+2) [17, 18]. Also, with current criteria, patients with ANCA-negative GPA would hardly be included in clinical trials. Further, even after the participation of more than 30 countries worldwide, some population groups were underrepresented (e.g., Africa and South America) [17, 18]. Finally, similarly to the ACR 1990 criteria, as these criteria were not intended to be used as diagnostic criteria, it is expected that they will perform poorly if used inappropriately for this purpose.

Other. An alternative approach to classification is based upon ANCA antigen specificity, that is PR3- or MPO-ANCA disease, rather than with the clinical phenotype. Although this classification correlates with a number of disease characteristics, such as genetic association, response to therapy, long-term outcome, and propensity for relapse, further investigation is needed to fully address the utility of this dual classification. Novel classification options using cluster analysis or using artificial neural networks are under investigation.

Although the ACR/EULAR criteria, the EMA algorithm, and the CHCC nomenclature system have been widely used to standardize research studies, their use for diagnosis in daily clinical practice is not recommended. These criteria may, however, be of utility for clinical practitioners to identify key disease features. The development of diagnostic criteria in GPA is an unmet need that has been hampered by factors such as the absence of a diagnosis gold standard, the wide and heterogeneous presentation of the disease, and legal and financial implications.

Treatment

After a prompt diagnosis, rapid initiation of treatment is needed. Early induction of remission with highly potent immunosuppressants is used to prevent organ damage, which is then followed by maintenance of remission aimed to prevent relapses and drug toxicity. The choice of therapy should be individualized based on factors such as age, clinical phenotype, disease severity, serologic profile, presence of comorbidities, and patient preferences [19, 20].

Induction to remission. Treatment of severe GPA (e.g., scleritis, alveolar hemorrhage, rapidly progressive glomerulonephritis) consists in high-dose glucocorticoids (GC) and rituximab or cyclophosphamide, which lead to remission in 50–90% of patients [19, 20]. Reduced GC tapering regimens and lower starting prednisone doses are now mainly recommended [19, 20]. C5a receptor inhibitor, avacopan, is a novel option used as adjunctive GC-sparing therapy. The use of plasma exchange remains highly controversial and is only routinely indicated in the overlap of ANCA vasculitis and anti-GBM disease, although it may be beneficial in severe NCGN. For non-severe disease (e.g., limited ENT, cutaneous, or articular involvement), treatment is based on either rituximab, methotrexate, or mycophenolate mofetil.

Maintenance of remission. Standard of care includes low-dose GC in combination with rituximab administered every 4-to-6 months. Azathioprine, methotrexate, or mycophenolate mofetil are less efficient alternative options. The optimal duration of maintenance therapy needs to be individualized.

Prognosis

GPA may be associated with increased morbidly and mortality. Permanent morbidity due to organ damage caused by vasculitis (e.g., ESKD, chronic peripheral neuropathy), granulomatous inflammation (e.g., chronic sinus dysfunction, destructive nasal deformity, tracheal stenosis), or treatment-related adverse effects (e.g., infections, osteoporosis, diabetes, or malignancies) will develop in almost all patients. Relapses occur in 38–54% of GPA cases and are associated with substantial risk of cumulative damage. Although survival has increased, there is still a 3.7–4.8-fold increased risk of death in patients with ANCA vasculitis when compared to general population. Patient survival at 1 and 5 years has been reported to be 88% and 70–78%, respectively. Main causes of death include infections, active vasculitis, cardiovascular events, and malignancy.

Conclusions

The diagnosis of GPA remains a clinical challenge. The combination of upper and lower respiratory tract granulomatous lesions and systemic vasculitis, with ANCA directed against PR3 is highly suggestive of the disease. Although improved treatment strategies have led to reduction in mortality, GPA is still associated with frequent relapses and long-term morbidity derived from the disease itself and its treatment, which may highly impact the quality of life of patients.

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Eosinophilic Granulomatosis with Polyangiitis (EGPA, Churg–Strauss)

19

Yann Nguyen and Loïc Guillevin

Abstract

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly called Churg–Strauss syndrome, is a systemic necrotizing vasculitis of small- and medium-sized vessels, characterized by asthma and blood eosinophilia. It usually occurs in individuals with preexisting asthma, and involves the skin, lungs, and peripheral nerves. Anti-myeloperoxidase antineutrophil cytoplasm antibodies are detected in a third of the patients; positivity or negativity of those autoantibodies seems to distinguish two phenotypes, with different clinical characteristics and prognoses. The Five-Factor Score (FFS) is an assessment of poor-prognosis factors, i.e., gastrointestinal tract, heart kidney, and/or central nervous system involvement(s). Although glucocorticoids and immunosuppressants have dramatically improved overall survival, relapse rates remain persistently high. Glucocorticoids should be prescribed to all patients, with adjunction of immunosuppressants (cyclophosphamide for induction and azathioprine or more recently developed agents for maintenance therapy) for those with severe/refractory disease and FFS-defined poor prognoses. And, now, novel advances in EGPA management include immunomodulatory and targeted therapies being evaluated to improve EGPA patients' prognoses: e.g., rituximab and anti-interleukin-5 agents for remission induction, and mepolizumab has been proven effective as maintenance therapy against relapses.

Keywords

Eosinophilic granulomatosis with polyangiitis · Eosinophilia · Systemic necrotizing vasculitis

Introduction

First described in 1951 by Jacob Churg and Lotte Strauss, and initially called Churg–Strauss syndrome, eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic necrotizing vasculitis of small- and medium-sized vessels. EGPA is classified as an antineutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV), even though ANCAs are not always detected. Its main characteristics are asthma, blood eosinophilia, and extrapulmonary manifestations [1–3]. Recent advances have contributed to better understanding of EGPA pathophysiology and its clinical phenotypes. Moreover, several novel immunomodulatory drugs and targeted biotherapies have broadened therapeutic options. Herein, EGPA pathophysiology, epidemiology, clinical manifestations, prognosis, and management, including newer therapies, are reviewed.

Pathophysiology

Genetic predisposition and immune dysregulation seem to be implicated in EGPA pathogenesis, which remains poorly elucidated, and many factors might be involved in its development.

Genetic Predisposition

Associations between specific human leukocyte antigen (*HLA*) alleles and EGPA have been identified in genetic studies. Vaglio et al found the *HLA–DRB4* gene to be associated with EGPA in patients harboring an *HLA–DRB1*04*, *HLA–DRB1*07* or *HLA–DRB1*09* allele (odds ratio (OR) 2.49 [95% confidence interval (CI) 1.58–3.09]) [4]. The likelihood of developing vasculitic manifestations of EGPA was significantly enhanced by *HLA-DRB4*-gene carriage ($P = 0.001$). Compared to healthy controls, EGPA patients had a lower *HLA–DRB3*-gene frequency (OR 0.54 [95% CI

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0.35–0.84]). A genome-wide-association study (GWAS), conducted on 676 EGPA patients and 6809 healthy controls from nine European countries, found at least four loci associated with EGPA, independently of ANCA status [5]. EGPA comprises two genetically and clinically distinct syndromes. Anti-myeloperoxidase (MPO)-positive EGPA is an eosinophilic autoimmune disease that shares some certain clinical features and an *HLA-DQ* association with MPO-positive AAV, while ANCA-negative EGPA may originate from a mucosal barrier dysfunction. ANCA-negative EGPA was more genetically similar to asthma than MPO-positive EGPA. The ANCA-negative group alone was associated with genetic variants at the *GPA33* (glycoprotein A33) and *IL5/IRF1* (interleukin-5/interferon regulatory factor-1) loci. Both MPO-positive and -negative EGPA subgroups were clearly associated with *TSLP* (thymic stromal lymphopoietin), *BCL2L11* (B-cell lymphoma-2-like protein-11) and *CDK6* (*cyclin-dependent kinase-6*) genes, but, to date, merely suggestive evidence has been reported for *BACH2* (broad complex-tramtrack-bric a brac and Cap'n'collar homology-2), chromosome 10, and *LPP* (lipoma-preferred partner) genes [5].

Immune Dysregulation

Abnormal eosinophil proliferation and impaired apoptosis, along with the enhanced tissue toxicity attributed to eosinophil products, are thought to be key factors involved in EGPA pathogenesis.

Defective CD95 (Apo-1/Fas)-mediated apoptosis is apparently responsible for excessive eosinophil proliferation [6]. Circulating eosinophils in patients with active EGPA express less primary proapoptotic genes (e.g., *CASP2* (*caspase-2)*, *CARD4* (caspase recruitment domain family member-4), *BLC2L13* (mitochondrially localized protein with conserved B-cell lymphoma-2 homology motifs)) involved in NF-κB (nuclear factor-kappa B) regulation [7]. Exposure to the triggering factors (described below) that attack respiratory epithelial cells could lead to cytokine (e.g., IL25) production. The high IL25 concentrations in EGPA patients' blood may drive CD4+ T lymphocytes toward a skewed T-helper-cell type-2 (Th2) phenotype, thereby maintaining eosinophil proliferation via the cytokines synthesized by those cells [8]. Elevated levels of eosinophilic cytotoxic proteins (e.g., eosinophil peroxidase, eosinophil cationic protein) directly implicated in tissue damage are also found in EGPA patients' sera, urine, and tissues [9].

As in asthma patients, in EGPA patients' CD4+ T lymphocytes, mostly Th2 phenotype, are activated. Th2 cells synthesize IL4, IL5, and IL13, whose concentrations are also elevated in EGPA patients' sera and bronchoalveolar lavage (BAL) fluid [10]. IL5 is known to be implicated in eosinophil maturation and survival, and its expression is strongly associated with clinical EGPA-activity parameters (Birmingham Vasculitis Activity Score (BVAS), eosinophilia). Moreover, Th1 and Th17 immune-cell responses seem to be involved [11].

Although not yet fully elucidated, a precise B-cell role in EGPA pathogenesis is starting to gain attention [12, 13]. Patients with frequently relapsing EGPA had higher percentages of CD27+, CD80+, or CD95+ B cells and lower CD19+ B-cell rates [14]. During EGPA flares, the immunoglobulin G-4 (IgG4) level, a surrogate marker of B-lymphocyte activation, can be elevated [15]. Notably, ANCA-positivity, another indicator of B-lymphocyte activation, is found in only one-third of EGPA patients. Moreover, anti-MPO ANCAs were able to directly trigger EGPA pathogenesis in vitro and in mouse models [16, 17].

Epidemiology

Incidence and Prevalence

EGPA prevalence ranges between 7.3 and 17.8 cases/million inhabitants [18, 19], with an annual incidence of 0.9–2.4 cases/million inhabitants [20, 21]; those values are apparently similar in Europe, Japan, and the USA [19]. No evidence supports male or female sexual predominance.

Mean age at EGPA diagnosis is ~50 years [22], which is lower than for granulomatosis polyangiitis (GPA), microscopic polyangiitis (MPA), or polyarteritis nodosa (PAN). Childhood-onset EGPA is extremely rare, with fewer than 50 reported cases worldwide [23–25]; it is characterized by predominant pulmonary and cardiac involvements, and its attributed mortality is high (18%) [25].

Triggering Factors

The quasi-constant asthma prodrome has led to allergens being suspected EGPA triggers. However, allergies were documented in fewer than one-third of EGPA patients, when frequent allergens were systematically tested. That preexisting allergy rate is similar to that observed in the general population. Although molecules potentially able to trigger EGPA onset may still be unknown, allergens are not the only factors able to induce EGPA manifestations [26].

Many environmental factors have been suspected EGPA triggers, e.g., inhaled antigens (dark diesel fumes, grain dust, cereal dust, dust), desensitization or immunization [27, 28]. Among 43 serial EGPA patients, 19 had undergone desensitization and vaccines had been given to five during the month preceding vasculitis diagnosis [28]. Those exposures might have simply served as disease accelerators for patients with ongoing covert-but-undiagnosed EGPA, rather than true triggers. However, almost all patients had asthma before the onset of EGPA manifestations.

Some drugs, mainly leukotriene-receptor antagonists (e.g., montelukast and zafirlukast) or, more recently, anti-IgE antibodies (e.g., omalizumab) have been considered potential triggers; however, their true implication remains undetermined because they are often prescribed during glucocorticoid-tapering [29–33]. Notably, based on 79 EGPA participants, the results of a case–crossover analysis showed that montelukast was significantly associated with the risk of developing EGPA within 3 months (OR 4.5 [95% CI 1.5–13.9]) [30]. However, that association was not specific, since long-lasting β_2-agonists had increased risks of comparable significance and comparable risk ratios were attributed to oral glucocorticoids. Pertinently, indication for those agents to treat gradually worsening asthma could be responsible for the potentially confounding associations. Vaccination of EGPA patients remains controversial. Anecdotical, EGPA-flares postimmunization have been published [28].

Based on our prospective study on anti-H1N1 influenza vaccination [34], eosinophils were only moderately increased in one patient who experienced a neuropathy flare 3 days postinoculation, which could have been coincidental. Therefore, we routinely recommend fully vaccinating EGPA patients, even if vaccination should be delayed for flaring patients.

Clinical Manifestations

General Symptoms

Constitutional symptoms commonly precede overt systemic manifestations (Table 19.2). Notably, 38.9% of our EGPA patient series had fever and myalgias, 29.8% arthralgias, and 50% had lost weight (mean loss 7.8 ± 4.7 kg) [22].

Pulmonary

Asthma affects 91–100% of the patients, usually preceding systemic vasculitis (mean interval 9.3 ± 10.8 years), making it the major EGPA characteristic. Indeed, asthma is one of the American College of Rheumatology (ACR) classification criteria (Table 19.1) [2]. Asthma onset often starts around 30–40 years of age but childhood onset is not unknown. According to a study [42], the mean asthma-onset-to-first-vasculitis-manifestation interval was 9.3 years. Among asthmatics, EGPA incidence was 34.6 (range 21.4–53) cases/million person-years. Their asthma is usually severe and glucocorticoid-dependent. The results of a retrospective study on 157 EGPA patients indicated asthma was mild, moderate, or severe in 17%, 26%, or 57%, respectively [43]. Asthma severity tended to increase during the 3–6 months preceding overt systemic disease, and high-dose inhaled glucocorticoids and bronchodilators were required for all patients. Mean postbronchodilator FEV_1 (forced expiratory volume in 1 second) was 69.7 ± 24.9% of the predicted value, and postbronchodilator FEV_1/FVC (forced vital capacity) was <0.7 for 54% of tested patients.

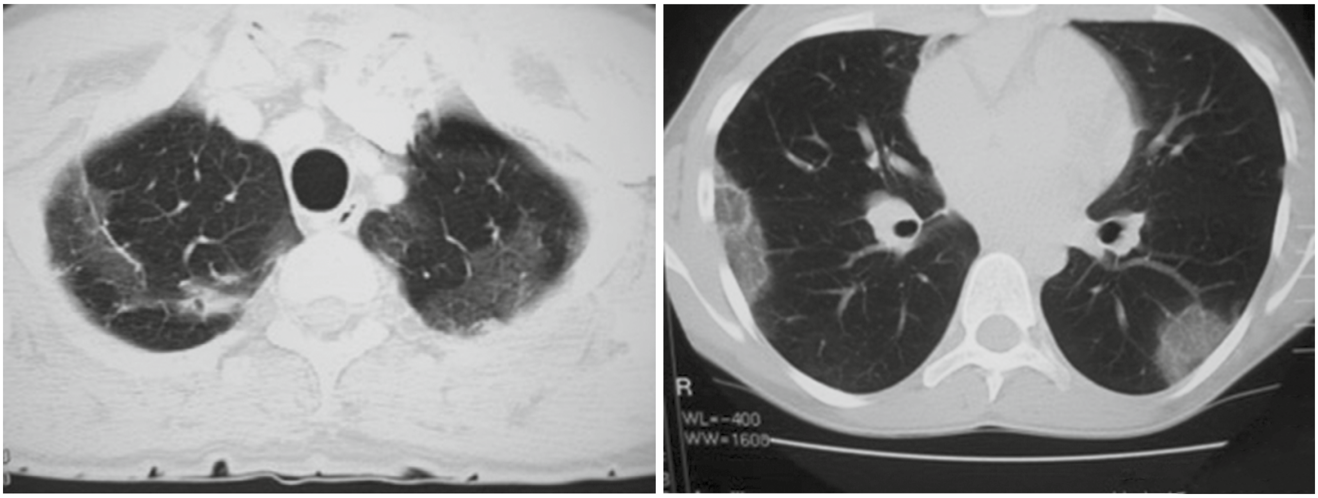
Table 19.1 1990 American College of Rheumatology classification criteria for EGPA (formerly Churg–Straus) [2]

Criterion	Definition
1. Asthma	History of wheezing or diffuse high-pitched rales on expiration
2. Eosinophilia	Eosinophilia >10% of white blood cell differential count
3. Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy (i.e., glove/stocking distribution) attributable to vasculitis
4. Pulmonary infiltrates, nonfixed	Migratory or transitory pulmonary infiltrates on radiographs (not including fixed infiltrates), attributable to systemic vasculitis
5. Paranasal sinus abnormality	History of acute or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses
6. Extravascular eosinophils	Biopsy including artery, arteriole, or venule, showing accumulations of eosinophils in extravascular areas

Compared to MPA, pulmonary vasculitis-induced alveolar hemorrhage is much less common in EGPA (4%) but can nonetheless be severe with massive hemoptysis (often associated with renal involvement: pulmonary–renal syndrome). However, most patients have mild episodes, with only bloody sputum or diagnosed by BAL. Although eosinophilic exudative pleural effusions have been described, histology of the rare pleural biopsies obtained showed signs of vasculitis with eosinophilic infiltrates [44]. Lung infiltrates, either uni- or bilateral, and transitory are common (38.6%) (Figs. 19.1 and 19.2); they often regress totally a few days after initiating glucocorticoids [45]. Extremely rare phrenic paralysis has been reported [46].

Ear, Nose, and Throat (ENT)

Maxillary sinusitis, notably one of the ACR classification criteria defining EGPA, is common (Table 19.2). Nasal polyposis and allergic rhinitis, found in 41% and 17% of EGPA patients, respectively, 22 must be distinguished from the destructive ENT manifestations of GPA. Polyposis and rhinitis in EGPA patients usually precede overt vasculitis. And despite their being considered EGPA symptoms, we think they reflect the underlying predisposition to the disease,



Figs. 19.1 and 19.2 Lung infiltrates during EGPA flare

Table 19.2 EGPA patients' clinical characteristics reported in the main published series

Characteristic	Chumbley et al. [35]	Lanham et al. [36]	Guillevin et al. [28]	Gaskin et al. [37]	Guillevin et al. [38]	Solans et al. [39]	Comarmond et al. [22]	Durel et al. [40]	Bettiol et al. [41]
Patient demographics									
Number included	30	16	43	21	96	32	383	101	203
Male/female sex ratio, *n*	21/9	12/4	24/19	14/7	45/51	9/23	199/184	43/58	87/116
Mean age (year)	47	38	43.2	46.5	48.2	42	50.3	49.2	59.1
[Range]	[15–69]		[7–66]	[23–69]	[17–74]	[17–85]	[35–66]		[38–57]
Clinical features									
General symptoms	–	–	72%	–	70%	69%	–	–	28%
Arthritis, arthralgias	20%	51%	28%	43%	41%		29.8%	68.3%	
Myalgias	–	68%	–	–	54%	–	38.9%	82.2%	
Allergic rhinitis and/or ENT involvement	70%	70%	21%	–	47%	–	48%	96%	71%
Asthma	100%	100%	100%	100%	100%	100%	91.1%	53.4%	92%
Pulmonary infiltrates	27%	72%	77%	43%	38%	53%	38.6%	53.5%	
Pleural effusion		29%	–	–	–	19%	8.9%	3%	
Skin involvement	67%		–	50%	51%	69%	39.7%	46.5%	
Purpura	–	48%	28%	–	31%	41%	22.5%	24.7%	7%
Nodules	27%	30%	21%	–	19%	6%	9.7%	8.9%	
Mononeuritis multiplex	63%	66%	67%	70%	78%	44%	46%	54.5%	23%
GI involvement	17%	59%	37%	58%	33%	38%	23.2%	25%	4%
CV involvement	16%	47%	49%	15%	30%	28%	27.4%	20.8%	5%
Renal involvement	20%	49%	16%	80%	16%	13%	21.7%	26%	2.5%

Values are expressed as percentages, unless stated otherwise. *ENT* ear, nose, and throat, *GI* gastrointestinal, *CV* cardiovascular making these patients more susceptible to developing vasculitis symptoms. Despite successfully treating a vasculitis flare, polyps and local symptoms can persist, which supports our underlying predisposition hypothesis.

Neurological

Peripheral neuropathies, mainly mononeuritis multiplex, are frequent, affecting 46–75% of EGPA patients [22]. In decreasing order of frequency, the following nerves were the most often affected: common peroneal, internal popliteal, then radial, cubital and/or median, and cranial [22].

Patients may experience paresthesia or sometimes painful hyperesthesia before motor or sensory deficits appear. When moderate, only superficial sensitivity is involved.

Although peripheral neuropathy is not an FFS poor-prognosis factor associated with mortality [47], its sequelae may indicate poorer functional outcome. Indeed, recovery is long and unpredictable. Motor-symptom disappearance with functional recovery is the more common evolution, but sensory symptoms can be definitive, leaving functional recovery often partial and unpredictable. Pain, paresthesia, and hypoesthesia can be major disabilities for patients, and require therapeutic escalation.

The central nervous system is rarely involved (5.2% in our series [22]) but, when present, reflects cerebral vasculitis. Clinical manifestations (e.g., seizures, hemiplegia, coma, brain hemorrhage) are nonspecific. Magnetic resonance imaging (MRI) is more sensitive to identify cerebral vasculitis, with T2-weighted cortical and subcortical signals. The central nervous system was no longer considered a poor-prognosis factor in the revised FFS [47], mainly because the too small number of patients precluded reaching statistical significance.

Cutaneous

EGPA skin manifestations affect 40–70% of patients, with the most frequent being vascular purpura (40–70%) of the lower limbs. Subcutaneous nodules are often symmetrical, red, and predominantly affect fingers, elbows, and upper limbs; they occur in 10–30% of EGPA patients. Skin nodules can also appear on the forehead.

When biopsies are obtained, histological findings can include non-EGPA-specific extravascular granuloma(s), also seen in inflammatory bowel diseases or other vasculitides. Raynaud's phenomenon, livedo reticularis, urticarial, or gangrenous necrotic lesions are other possible cutaneous manifestations of EGPA.

Gastrointestinal

Gastrointestinal involvement is a FFS poor-prognosis item [47, 48]. Its symptoms—abdominal pain (30–60%), diarrhea, nausea, vomiting, and/or intestinal hemorrhage—are often nonspecific. Bowel perforation is associated with high mortality rates [49]. Surgery may be necessary for patients with ischemic colitis or mesenteric ischemia [38]. When biopsies are obtained, histological findings can include extravascular granulomas, sometimes mimicking pseudopolypoid lesions, vasculitis, and/or eosinophilic infiltrates. As described for eosinophilic syndrome and EGPA, esophageal and sometimes other gastrointestinal segments' wall-thickening could signal eosinophilic infiltration that disappears under glucocorticoids.

Cardiac

Heart involvement, another prognostic FFS item, is strongly associated with death [47] and is the primary cause of EGPA patients' mortality. It manifests as pericarditis (15.1%), arterial hypertension, valvopathy, eosinophilic myocarditis, and/or congestive heart failure (16.4%) [22]. Indeed, 31% of the deaths of our EGPA series were attributed to cardiac involvement [22]. Still, its frequency may be underestimated. Detailed cardiac work-ups of 32 ambulatory EGPA patients considered to be in remission found cardiac involvement in 62%: 66% with electrocardiogram (EKG) abnormalities, 60% had echocardiographic defects, and 62% with MRI anomalies; pertinently, only 26% of those patients were symptomatic [50]. At present, it seems appropriate that only clinical manifestations be taken into account as criteria for therapeutic escalation. We do not recommend a regimen combining high-dose glucocorticoids, immunosuppressants, and/or biotherapies when minor electrocardiographic, echocardiographic, or cardiac laboratory-value anomalies are present.

ANCA-positive patients experience less frequent cardiac involvement [38]. Pathophysiologically, cardiac manifestations are derived from coronary vasculitis, extravascular granuloma(s), and cardiac eosinophilic interstitial infiltrate(s).

Renal

Renal involvement affects 16–22% of EGPA patients, much less frequently than other AAVs. Among our EGPA-patient series, only 12.8% had significant proteinuria >0.4 g/24 h; mean ± standard deviation (SD) creatininemia for the entire series at diagnosis was 89.1 ± 38.6 μmol/L (1.01 ± 0.44 mg/dL) [22]. When renal biopsies were obtained, histological findings included focal or diffuse crescentic glomerulonephritis, and less frequent eosinophilic infiltrates, granuloma(s) or renal vasculitis [51]. Glomerulonephritis in EGPA patients is usually associated with anti-MPO ANCA-positivity. Ureteral stenosis has been described only rarely [52].

Ophthalmological

Ophthalmological ischemic vasculitis, uveitis, episcleritis, and/or orbital inflammatory pseudotumor with conjunctival involvement are rare EGPA manifestations that have been reported [53].

Complementary Investigations

Blood eosinophilia is an EGPA constant and diagnostic criterion. The mean ± SD eosinophil count at diagnosis for our series [22] was 7569 ± 6428/mm^3, but counts exceeding 50,000/mm^3 have been reported [54]. Eosinophil counts may oscillate rapidly and several days of EGPA treatment suffice to achieve a decline. Subsequently, usually during glucocorticoid tapering, eosinophilia rises can occur without concomitant new clinical manifestations; pertinently, isolated eosinophilia cannot be considered sufficient to diagnose a relapse.

An inflammatory syndrome is documented in ~80% of EGPA patients; for our series, the mean C-reactive protein was 66.9 mg/L and 56.1% had an elevated 1st-hour erythrocyte sedimentation rate [22].

About one-third of EGPA patients are ANCA-positive; most of those ANCAs generate perinuclear immunofluorescence-labeling (P-ANCA) and enzyme-linked immunosorbent assay determined ~70% of them were directed against MPO. No antinuclear antibodies are found but rheumatoid factor can be detected [55]. When ANCA is anti-proteinase-3 (PR3)-specific, the clinician should remember that asthma can be a disease independent of vasculitis and eosinophilia can be a manifestation of other vasculitides, e.g., GPA or PAN. It can thus be considered likely that anti-PR3-EGPA diagnoses are erroneous.

For patients with alveolar hemorrhage, red blood cells are seen in BAL fluid and the Golde score is elevated. In other contexts, BAL fluid can contain inflammatory cells, predominantly eosinophils. BAL fluids from a series of EGPA patients contained a mean of 296 leukocytes/mm^3 with a mean ± SD of 33 ± 29 eosinophils [43].

Histological findings have good sensitivity to confirm EGPA diagnoses [36, 38]. The most common biopsy sites are skin, nerve, and/or muscle. Although three types of lesions can be seen, they are rarely found simultaneously (<20% of EGPA patients): 1) necrotizing small-to-medium-sized–vessel vasculitis, with fibrinoid necrosis of the media and pleomorphic cellular, mainly eosinophil, infiltrate; 2) extravascular granuloma(s), with central necrosis and epithelioid cells, which, although quite typical of EGPA, are non-specific, as they are also observed in other vasculitides (e.g., GPA) or autoimmune diseases; and 3) eosinophil infiltration of arterial walls and adjacent tissues [56].

Among 157 EGPA patients, 58% had chest radiographic abnormalities at diagnosis, with consolidation (29%), ground-glass attenuation (29%), nodules or masses (9%), and/or pleural effusion(s) (10%); those lesions were frequently bilateral (58%) [43]. Chest computed-tomography (CT) scan can more precisely evaluate lung abnormalities, because it can visualize micronodules <3 mm (24%), bronchial wall-thickening (32%), ground-glass opacities (39%), and/or consolidation (28%) [43]. Angiography may help detect mesenteric vasculitis and it can reveal stenosis consistent with vasculitis. Microaneurysms are rare.

Echocardiography or cardiac MRI detected abnormalities in 38% of patients asymptomatic or without EKG abnormalities [50]. To date, for asymptomatic patients, the real interpretation of T1-weighted cardiac MRI abnormalities (e.g., centromyocardial, subepicardial, and/or subendocardial late gadolinium enhancement) remains unelucidated. Notably, a French series of 42 non-cardiomyopathic (diagnosed independently of MRI findings) EGPA patients—with or without MRI abnormalities—had comparable EGPA outcomes. Cardiac MRI should not be the only diagnostic investigation for cardiomyopathy [57, 58]. Sometimes, distinguishing EGPA cardiomyopathy from underlying ischemic cardiopathy can be achieved with coronary arteriography.

Diagnosis

Diagnostic Criteria

As stated above, concomitant observation of all three histological EGPA lesions occurs quite rarely, meaning that EGPA diagnosis remains clinical. In 1984, Lanham et al. used the following criteria to redefine EGPA [36]: asthma, blood eosinophilia >1500/mm^3, and at least two organs with manifestations suggestive of vasculitis [36]. However, those criteria were deemed insufficient because asthma onset can follow the vasculitic phase and blood eosinophil counts may fluctuate.

In 1990, the ACR published criteria for classification [2]. A patient diagnosed with vasculitis may be classified as having EGPA when at least four of the following criteria are present (Table 19.1): asthma, eosinophilia (>10% of white blood cell count), mononeuropathy or polyneuropathy, pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils.

More recently, the Chapel Hill Consensus Conference Nomenclature [3] defined EGPA as an "an eosinophil-rich and necrotizing granulomatous inflammation, frequently involving the respiratory tract, and necrotizing vasculitis predominantly affecting small-to-medium–sized vessels, and associated with asthma and eosinophilia."

The 2022 ACR/European Alliance of Associations for Rheumatology (EULAR) classification criteria for EGPA introduced a weighted-symptom method for patient classification but the criteria advanced are not more useful than those given earlier in "classification" papers [59]. In contrast, their probable misuse for diagnosis could lead clinicians to erroneously consider an EGPA diagnosis for many patients with obstructive lung disease and sinonasal polyposis, without other extrapulmonary signs [60].

Pertinently, all those criteria are intended for classification of vasculitides that have already been diagnosed; they are most often applied for clinical studies.

We think that EGPA can be diagnosed with a high level of confidence when a patient has asthma, eosinophilia and extrapulmonary manifestations, and histological proof of vasculitis and/or anti-MPO-positive ANCA (Figs. 19.3 and 19.4). Without those items, that combination of clinical symptoms is accepted for a probable diagnosis, albeit with some degree of uncertainty. Some authors now apply the MIRRA-trial [61] criteria for EGPA diagnosis: asthma plus eosinophilia (>1.0 × 10^9/L and/or >10% of leukocytes); and at least two of the following: histopathological evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration or eosinophil-rich granulomatous, inflammation neuropathy, mono- or poly-motor deficit or nerve-conduction abnormality, pulmonary infiltrates, non-fixed, sinonasal abnormality, cardiomyopathy (established by echocardiography or MRI), glomerulonephritis (hematuria, red cell casts, proteinuria), alveolar hemorrhage (BAL documented), palpable purpura, anti-MPO or -PR3 ANCA-positivity. Such criteria have strong diagnostic value but are more "ideal or theoretical" than practical for daily clinical use because one extrapulmonary manifestation, like mononeuritis multiplex or vascular purpura, in addition to asthma and eosinophilia, can suffice for diagnosis. We also question the value of anti-PR3 antibodies, which would rather be diagnostic for GPA, which can also be associated with eosinophilia, and sometimes occurs coincidentally in asthmatic patients.

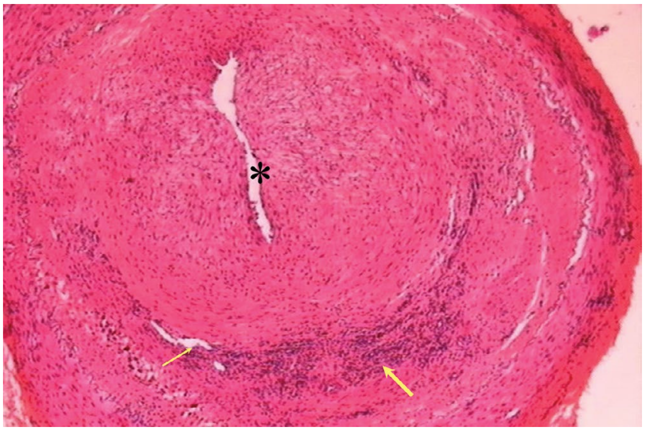


Fig. 19.3 Temporal artery biopsy in a patient with EGPA: Partial occlusion of arterial lumen (*). Inflammatory infiltrates surrounding thrombus

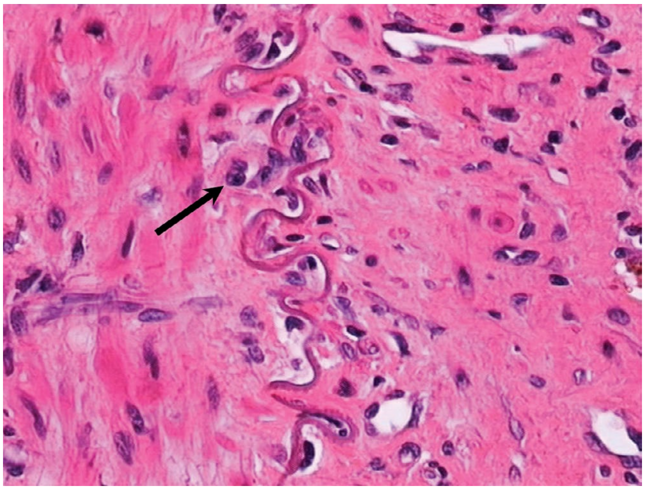


Fig. 19.4 Lymphocytes and histiocytes are found around internal lamina elastica (arrow)

Diagnostic Criteria for Relapse or Flare

When patients relapse long after the first flare while not taking any treatment other than low-dose oral or inhaled steroids at the time of relapse, diagnostic criteria are similar to those described above. When a flare is suspected in a patient taking oral glucocorticoids, sometimes in combination with immunosuppressants and/or anti-IL5, diagnosis of a relapse is often difficult, especially for patients with an asthma flare and only eosinophilia. In our opinion, to diagnose an EGPA relapse, the patient must have systemic manifestations. An asthma flare is not sufficient to diagnose an EGPA flare. Considering an asthma exacerbation a synonym for EGPA flare or relapse overdiagnoses them.

Differential Diagnosis

Before vasculitic manifestations appear, it can be difficult to distinguish EGPA from eosinophilic asthma or allergic bronchopulmonary aspergillosis. After their appearance, EGPA must be distinguished from other systemic vasculitides, especially PAN and GPA. Although eosinophilia may also be associated with GPA, EGPA's distinguishing characteristics include asthma, nondestructive ENT manifestations, and anti-MPO specificity of detectable ANCAs.

The etiology of idiopathic, chronic, eosinophilic pneumonia, as indicated by its name, remains unelucidated. It is a rare disease with nonspecific respiratory symptoms and eosinophilia that responds well to oral glucocorticoids [62–64]. Although it can be confounded with EGPA, no vasculitic and extrapulmonary signs are associated, meaning its diagnosis is made by progressive exclusion of other possibilities.

Hypereosinophilic syndrome (HES) is a more difficult entity to exclude from the differential diagnosis, because it too may also be associated with cardiopathy, nerve involvement, and/or pulmonary manifestations. However, those clinical similarities are overridden by HES having no vasculitic symptoms or any of the histological findings typical of EGPA [65]. HES has two readily differentiated variants: lymphocytic, predominantly affecting skin-and-soft tissue, attributed to abnormal $CD3^{-}CD4^{+}$ T-cell subsets synthesizing IL5 [66]; and myeloid, characterized by specifically elevated tryptase and vitamin B_{12} levels, signs enabling HES exclusion. Myeloid HES diagnosis can be confirmed by searching for mutations in *FIP1L1–PDGFRA* (FIP1-like-1–platelet-derived growth factor receptor-α fusion tyrosine kinase) and *JAK2* (Janus kinase-2) genes [67].

To exclude differential diagnoses, the EGPA Consensus Task Force experts recommended complementary investigations: toxocariasis and human immunodeficiency virus serology, the search for *Aspergillus* spp. in sputum and/or BAL specimens, anti-IgE and IgG specific to *Aspergillus* spp., tryptase and vitamin B_{12} levels, peripheral blood smears to look for dysplastic eosinophil blasts and thoracic CT scan [68].

Asthma with eosinophilia can also sometimes be another differential diagnosis of EGPA. When a patient has no extrapulmonary manifestations, it is difficult to distinguish between the first EGPA manifestations and asthma with eosinophilia. Indeed, extrapulmonary manifestations of a first EGPA flare might not occur until after a first phase consisting of asthma and eosinophilia. EGPA can be diagnosed early when ANCAs are detected but otherwise the diagnosis is usually delayed. For a patient with diagnosed EGPA, distinguishing between a flare without extrapulmonary manifestations and asthma with eosinophilia is often difficult. Each diagnosis must be made individually; however, EGPA flares are probably overdiagnosed when asthma manifestations with eosinophilia reappear as the only symptoms. EGPA relapses are frequently overdiagnosed, leading to treatment escalation based on clinical manifestations with a low level of evidence. Some recent recommendations support this ambiguity [59].

Prognoses and Outcomes

Glucocorticoids and immunosuppressants have revolutionized the prognosis of EGPA: the 5-year survival rate has risen from 10% in the 1950s to ~90% today [22].

Notably the presence or absence of identified prognostic factors can impact these patients' prognoses. Initial multivariate analyses of characteristics and outcomes of 260 PAN and 82 EGPA patients were used to formulate the original prognostic FFS [48]. The presence of each of the following items was accorded 1 point: proteinuria >1 g/day; gastrointestinal bleeding, perforation, infarction and/or pancreatitis; renal insufficiency (with creatininemia >1.58 mg/dL or 140 μmol/L); central nervous system involvement; and cardiomyopathy. Summation of the assigned points yielded the FFS; scores of 0, 1, or 2 were associated, respectively, with 5-year mortality rates of 12%, 26%, and 46%.

The revised FFS 15 years later, based on a new analysis of 1108 vasculitis patients, included 230 with EGPA [47]. The analysis-retained items were: serum creatinine >150 μmol/L, severe gastrointestinal involvement, myocardial involvement, age >65 years (each accorded +1 point), and the presence of ENT manifestations (–1 point). A revised FFS of 0, 1, or 2, respectively, was associated with 5-year mortality rates of 9%, 21%, or 40%.

Use of the revised FFS can contribute to identifying EGPA patients at high risk of death who require aggressive therapy with immunosuppressants. All current therapeutic recommendations support making treatment choices based on the revised FFS [69].

For our series, the most frequent causes of death, in descending order, were heart-related (i.e., cardiac insufficiency, arrhythmia and/or myocardial infarction (31%)), malignancies (11%), infections (11%), respiratory failure (severe asthma or end-stage chronic obstructive pulmonary disease (9%)), or active vasculitis (9%) [22].

EGPA relapses are defined as the new appearance, recurrence or worsening of clinical vasculitis manifestations that require adjunction, change or intensification of the glucocorticoid and/or other immunosuppressant dose(s) [68]. Asthma exacerbation and/or sinusitis alone are not sufficient to diagnose an EGPA flare. The EGPA Consensus Task Force formulated that recommendation to reduce the number of overdiagnoses. Considering all patients in our series, the 5-year relapse-free survival rate was 78.6% (95% CI 64.3–84.3); 18% experienced asthma flares, sinusitis, and/or enhanced eosinophilia levels, justifying prolonged glucocorticoid use among 85% of them [22]. EGPA relapses remain a major issue in search of a solution.

Even though progress has indeed been made in attaining EGPA remissions, asthma-symptom persistence remains a major problem. Despite treatment, a series of 157 patients' asthma severity remained unchanged months and even years after EGPA had been diagnosed [43]. At diagnosis, 3 years, and the most recent visit, respectively, 38%, 30%, and 46% had persistent airflow obstruction, and 57%, 48%, and 56% of them had severe asthma despite inhaled and often oral glucocorticoids [43]. Pertinently, persistent respiratory symptoms impact long-term management and morbidity.

Phenotypes According to ANCA Status

ANCA-positivity or -negativity imposes significantly different EGPA clinical findings and prognoses (Fig. 19.5). Two phenotypes have been defined [70, 71]. Based on the analysis of a series of 93 patients, ANCA-positivity was associated with more frequent vasculitis-associated symptoms: renal involvement (51.4% vs 12.1%; $P < 0.001$), pulmonary hemorrhages (20% vs 0%; $P = 0.001$), purpura and/or mononeuritis multiplex [70]; while ANCA-negativity was associated with more frequent eosinophilic infiltrates: lung infiltrates (60.3% vs 34.2%) and/or cardiac involvement (22.4% vs 5.7%; $P = 0.042$). Similar results were obtained after analysis of another series of 112 EGPA patients: ANCA-positivity was associated with more frequent renal involvement (35% vs 4%), peripheral neuropathy (84% vs 65%), and biopsy-proven vasculitis [71]. Prognoses for our patient series differed according to ANCA phenotype, with positivity being associated with more frequent relapses (35.2% vs 22.5%; $P = 0.01$) but fewer deaths (5.6% vs 12.5%; $P < 0.5$) [22].

As mentioned above, a recent GWAS on EGPA patients was able to identify—genetically and clinically—two subentities, based on ANCA-positivity with distinct genetic profiles [72]. Those findings indicate that more informative insights might be gleaned by stratifying EGPA patients in future clinical trials based on their ANCA status or genetic parameters, if available.

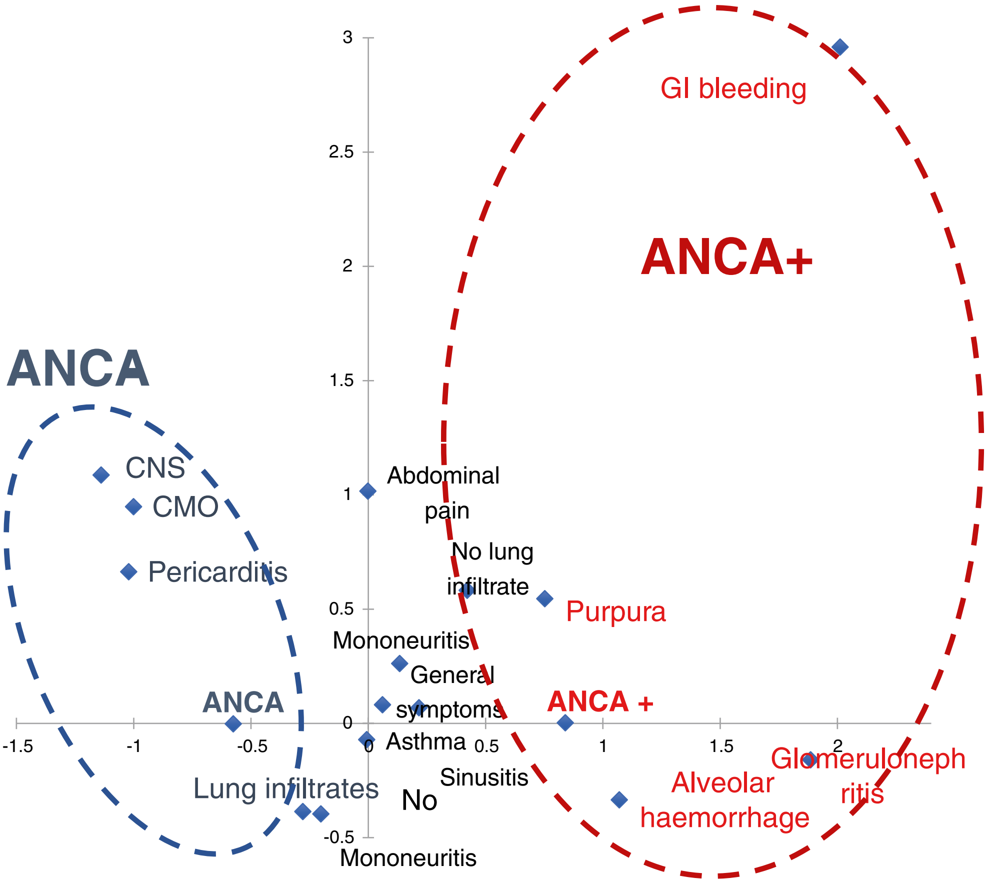


Fig. 19.5 Clinical symptoms of EGPA according to the presence or absence of ANCA

Treatment

Therapeutic Strategies

Available options continue to include glucocorticoids and immunosuppressants, and now targeted biotherapies. As for GPA and MPA, the EGPA regimen comprises remission-induction and maintenance phases. In 2015, the EGPA Consensus Task Force published recommendations for the evaluation of EGPA patients and their management [68]. EGPA treatment is complex because asthma and/or ENT manifestations can persist even after vasculitis remission has been obtained, often requiring long-term glucocorticoids.

A personalized treatment strategy should be adapted to each EGPA patient's disease severity, organ involvement, prognosis, age, and comorbidities. The FFS was devised to assess disease prognosis but it's application to adapt the therapeutic regimen is now largely used by international recommendations [73].

For patients without poor-prognosis factors (initial FFS = 0), we recommend first-line therapy with glucocorticoids alone, as they have been shown to effectively and safely induce and maintain remissions. The prospective, randomized, CHUSPAN trial enrolled 72 patients with newly diagnosed EGPA without poor-prognosis factors. In that trial, glucocorticoids alone achieved remission for 93%, with 97% 5-year survival. However, 35% relapsed, mainly during the first year of treatment, and eventually immunosuppressant adjunction was required to limit the frequency of relapses and perhaps their severity [74].

However, for good-prognosis patients, the efficacy of immunosuppressant adjunction remains controversial. Results of the randomized, prospective CHUSPAN2 trial showed that azathioprine adjunction to glucocorticoids did not improve the remission rate or lower the relapse rate [75] and, pertinently, did not contribute notably to steroid-sparing. The EULAR/ERA-EDTA (European Renal Association–European Dialysis and Transplant Association) recommendations for the management of small- and medium-vessel vasculitis did not stratify treatment guidelines according to the FFS, despite the results of several prospective trials clearly highlighting its pertinence [76]. Controlled-trial findings did not support the use of other immunosuppressants (e.g., methotrexate or mycophenolate mofetil) considered possible therapeutic options, and azathioprine obtained better outcomes.

For EGPA patients with poor-prognosis factors (i.e., with FFS≥1) and/or other life-threatening manifestations, even those not included in the initial or revised FFS (i.e., possible blindness due to eye involvement, severe alveolar hemorrhage and/or fulminant mononeuritis multiplex), combining an immunosuppressant with glucocorticoids is recommended [68].

Remission-Induction Regimen

The induction phase is intended to achieve, as rapidly as possible, clinical remission, defined as the absence of clinical vasculitis manifestations. Glucocorticoids are essential to achieve EGPA remission. The initial dose should be prednisone (~1 mg/kg/day or its equivalent of methylprednisolone) for 2–3 weeks, followed by gradual tapering. Initial life-threatening symptoms require rapidly acting intravenous methylprednisolone pulses (usually 7.5–15 mg/kg/day on days 1–3) at treatment onset. A response to glucocorticoids is usually seen quite quickly, with rapid attenuation of vasculitis manifestations, asthma symptoms, and diminished eosinophilia. No standard regimen is consensual for glucocorticoid tapering but the dose should be gradually decreased to the lowest effective dose until withdrawal, if possible. However, the steroid-dependent asthma of EGPA patients often necessitates long-term prednisone. A daily dose <7.5 mg could be targeted to avoid glucocorticoid-related adverse events (AEs) but AEs may occur even at low doses, and steroid toxicity is cumulative.

Cyclophosphamide has been the most investigated immunosuppressant to be added when manifestations make such adjunction essential. A prospective study on 48 EGPA patients with FFS≥1 evaluated cyclophosphamide efficacy, comparing 12 vs 6 pulses, both with glucocorticoids but no subsequent maintenance therapy was prescribed [77]. No significant difference was found between the two regimens and the complete remission rate for all patients was 78.5%. However, the high relapse rates (28.6% vs 66.7% for the 12- vs 6-pulse groups) indicate the need for maintenance therapy. Intravenous (IV) pulses or continuous oral cyclophosphamide (2 mg/kg/day) are deemed equally effective, by analogy to the induction regimen prescribed for GPA and MPA in our 1997 prospective trial [78], subsequently confirmed by the CYCLOPS trial [79]. However, oral intake leads to higher cumulative cyclophosphamide doses and more severe leukopenia. According to a post-hoc, long-term, follow-up analysis, IV pulses were associated with a higher relapse risk (39.5% vs 29.8%, hazard ratio 0.50 [95% CI 0.26–0.93]; $P = 0.029$) but not with increased mortality [80]. Importantly, IV pulses might have the potential advantage of favoring compliance.

By analogy with other AAVs, the standard-of-care has since become 6 cyclophosphamide pulses for induction (3 infusions at 0.6 g/m^2 or 15 mg/kg every 2 weeks, followed by 3–6 additional pulses at 15 mg/kg or 0.7 g/m^2 every 3 weeks) followed by maintenance therapy [68].

The prospective, randomized, CORTAGE trial on 108 patients ≥65 years old with AAVs (including 14 with EGPA) evaluated fixed, lower-dose, IV cyclophosphamide pulses (500 mg/m^2 every 2–3 weeks until remission) vs the standard regimen with limited glucocorticoid exposure [81].

Remission rates between the two arms did not differ but fewer serious AEs were observed with the "lower-dose" regimen.

New Drugs Now Available to Treat AAVs

Rituximab

Rituximab is a chimeric monoclonal antibody directed against CD20-expressing B lymphocytes. It has demonstrated efficacy and safety to induce GPA and MPA remissions and maintain them [12, 13], but rituximab use to treat EGPA has been limited to case reports and case series [82–84]. Rituximab seems to effectively and safely induce remission, mainly for ANCA-positive patients, but bronchospasms after the first infusion were reported [85]. The prospective, randomized REOVAS trial, conducted by the French Vasculitis Study Group, evaluated rituximab's remission-induction efficacy in patients stratified according to their initial FFS. Trial results showed that rituximab's ability to induce vasculitis remission was not superior to that of the conventional therapeutic strategy [86]. Too little data are available to analyze with sufficient power and, thus, to identify a different response to rituximab according to ANCA status. The absence of rituximab superiority over cyclophosphamide for induction could influence therapeutic choices in the context of the COVID-19 pandemic. The profound and sustained rituximab-induced immunodepression in AAV patients has engendered an increased number of deaths, thereby limiting rituximab's indication when the benefit/risk ratio is not met [87, 88].

Mepolizumab and By Extension Other Anti-IL5 Agents

Moosig et al published the first results showing mepolizumab efficacy for remission induction in 2011 [89]. Since that time, no prospective series of patients has been reported and the only prospective study evaluating mepolizumab for remission induction was organized by the French Vasculitis Study Group, which is still recruiting patients. Despite the lack of evidence, the ACR has recommended mepolizumab as first-line therapy for EGPA [69], which is highly debatable, because convincing data demonstrating that mepolizumab is as effective on extrapulmonary manifestations of EGPA as pulmonary symptoms are lacking.

Maintenance Therapy

Once remission has been attained, a regimen to maintain it should be prescribed for poor-prognosis patients with FFS ≥1, as their relapse risk remains high (73.8–85.7%) [77]. Maintenance therapy should be initiated 2 weeks after the last cyclophosphamide pulse or a few days after stopping oral cyclophosphamide.

Quite a few immunosuppressants have been prescribed as maintenance therapy but, unlike GPA or MPA, no randomized trial has compared them as a better strategy for EGPA. In analogy to GPA and MPA, azathioprine can be prescribed, initially at 2 mg/kg/day, but the dose can be adjusted to the clinical response and toxicity.

Because mycophenolate mofetil is inferior to azathioprine for GPA and MPA remission-maintenance therapy, it is not prescribed very often [90].

Based on a prospective trial for GPA and MPA remission-maintenance therapy, methotrexate seems to be an acceptable alternative to azathioprine [91]. The initial methotrexate dose should be 0.25 mg/kg/week.

Although the optimal maintenance-therapy duration has not yet been determined, it must be given for at least 18–24 months after remission. To date, no consensus criteria have been formulated for completely stopping treatment. However, in a study on the long-term outcomes of 118 EGPA patients, relapses occurred a mean of 2 years after induction had begun, i.e., when immunosuppression had been terminated for almost all patients, suggesting that long-term immunosuppressive therapy might be needed [92].

The 1-year, phase III clinical MIRRA trial enrolled 136 patients with relapsing or refractory EGPA [61]. Its results indicate that mepolizumab addition to standard care can prevent EGPA relapses. Mepolizumab's glucocorticoid-sparing capacity was also noteworthy: during weeks 48–52, 66% of patients in the placebo group took glucocorticoids at a dose >7.5 mg daily, as opposed to 41% of the mepolizumab recipients; moreover, only 3% of placebo-treated patients were completely off steroids compared with 18% of those given mepolizumab. Mepolizumab at a monthly dose of 300 mg, and probably other anti-IL5 drugs, can effectively prevent relapses and now assume a larger place in the maintenance treatment of EGPA. Lower doses of mepolizumab (100 mg/month) or benralizumab (30 mg/2 months) have been shown to effectively control asthma and reduce corticosteroids. They have empirically been prescribed to prevent EGPA flares but that strategy is not proven by controlled-trial results.

Other Treatments

Outcomes described in case reports and case series indicate that IV immunoglobulins can be given as second-line-therapy for EGPA flares, after other therapeutics failed [93, 94].

As for GPA and MPA, therapeutic plasma exchanges are an option for selected ANCA-positive patients with rapidly progressive glomerulonephritis or severe pulmonary–renal syndrome and alveolar hemorrhage [95], even though their long-term benefits remain unknown [96]. It should be kept in mind that plasma exchanges achieve short-term efficacy and a long-sustained effect seems unlikely.

Although interferon-alpha successfully induced EGPA remission, its ability to prevent major relapses seems limited and, in light of its numerous AEs, it is best not to prescribe it [97, 98].

Omalizumab, a monoclonal antibody targeting IgE, can be given to treat allergic asthma and allergic rhinitis, but its effectiveness against EGPA remains contradictory. Its activity against active disease has been suggested but the authors of some case reports identified a possible association between omalizumab administration and EGPA onset [32, 33, 99, 100]. The results of a more recent French retrospective study on 17 EGPA patients indicated that omalizumab might have a glucocorticoid-sparing effect: the median prednisone dose could be lowered from 16 mg/day initially to 9 mg/day at month 12 [101]. However, eight patients stopped taking omalizumab because of remission (12.5%), adverse events (12.5%), refractory disease (25%), and relapse (50%).

Efficacy of mepolizumab, an anti-IL5 monoclonal antibody, was demonstrated in a double-blind, multicenter, phase-3 trial on 136 patients with relapsing or refractory EGPA taking a stable prednisone dose for at least 4 weeks [61]. Mepolizumab obtained significantly more accrued weeks of remission than placebo (28% vs 3% of the participants had ≥24 weeks of accrued remission; OR 5.91 [95% CI 2.68–13.03]; $P < 0.001$), and glucocorticoid-tapering was possible.

Prevention of Adverse Events

The improved EGPA prognosis has transformed this vasculitis into a chronic relapsing disease for most patients taking long-term glucocorticoids, thereby elevating the importance of other therapeutic support, e.g., prevention of glucocorticoid-related complications (i.e., calcium and vitamin D supplementation, and bisphosphonates).

Prevention of cyclophosphamide-associated serious AEs (e.g., hemorrhagic cystitis and gonadal toxicity) warrants prophylaxis prescription, along with co-trimoxazole or pentamidine-aerosol against *Pneumocystis jiroveci* pneumonia.

As stated above, despite vaccination being suspected of triggering EGPA [28], the enhanced risk of potentially fatal infections while on immunosuppressants strongly favors immunizing patients with inactivated vaccines against influenza and *Streptococcus pneumoniae*. According to a prospective, open, monocenter vaccine phase III study on 199 patients with autoimmune diseases, including 20 with EGPA, seasonal flu vaccine was safe and effective, with 80.3% of patients obtaining seroprotection (defined as hemagglutination-inhibition antibody titers ≥1:40 determined in serum samples obtained 3 weeks postinoculation) [34]. However, immunization effectiveness seemed to be sensitive to ongoing treatment, with seroprotection rates of 86.7%, 79.8%, and 60%, respectively, for patients with autoimmune diseases not taking any immunosuppressant, on immunosuppressants or receiving targeted biotherapy (including rituximab) [34].

Rituximab-treated AAV patients were enrolled in the PNEUMOVAS trial to receive an innovative, reinforced, anti-pneumococcal vaccine strategy based on two Pneumococcal 13-valent conjugate (PCV13) doses—on days 0 and 7—followed by a single dose of **Pneumococcal polysaccharide vaccine** (PPSV23) at month 5. That strategy significantly improved the antibody responses against *Streptococcus pneumoniae* compared to the standard regimen. However, study participants had GPA or MPA; none had EGPA. The trial conclusions can be extended to EGPA but are not supported by data. It is important to emphasize that, at month 6, patients in the reinforced-vaccination arm had mounted immune responses to 0–3, 4–6, 7–9, or 10–12 serotypes of, respectively, 56.3%, 28.1%, 15.6% and 0%, which are low rates against some serotypes [102]. Because AEs and EGPA flares have sometimes been observed postinoculation, we prefer vaccinating patients in remission and not during the acute phase of the disease [28].

In addition, patients treated with immunosuppressants, especially rituximab, are at high risk of severe forms of COVID-19 [103]. Hence, prevention strategies are strongly recommended. Pertinently, anti-COVID-19–vaccine immunogenicity could be compromised by their immunosuppressive treatments [104]. Should COVID-19 diagnosis be confirmed, an antiviral, like Nirmatrelvir, should be prescribed, in the absence of contraindications, particularly drug interactions [105].

Lastly, patients should be encouraged to avoid tobacco smoke and specific patient-education programs are strongly encouraged [106].

Conclusion

The past few decades have seen notable progress made in our understanding of EGPA—its pathophysiology and management—thereby improving patients' prognoses. MPO-positive or -negative ANCA-status is associated with defined clinical phenotypes, and their different clinical findings, prognoses, and genetic backgrounds are now being elucidated.

Unfortunately, EGPA-relapse rates remain high and, despite their potential AEs, long-term glucocorticoids remain a necessity for many patients. Further investigations are needed to improve the overall care of EGPA patients.

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Buerger's Disease

20

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Abstract

Buerger's disease (thromboangiitis obliterans or TAO) is a rare non-atherosclerotic vascular disease, characterized by a combination of segmental inflammation and thrombosis of medium- and small-sized arteries and veins both in the arms and the legs. The inflammatory process leads to severe ischemic rest pain, non-healing sores, ulceration, and gangrene of fingers and toes. The disease is more common in young males, though its incidence seems to be increasing among women. Buerger's disease is strongly associated with tobacco abuse in any form, which most probably triggers an autoimmune response. TAO does not fulfill, however, the criteria for a classical autoimmune disease, because no autoantigen has been clearly identified to date in the disease. Various sets of diagnostic criteria have been suggested over the years and the diagnosis requires the elimination of many other diseases. Absolute discontinuation of smoking remains the essential mode of therapy. New therapeutic modalities have been recently studied in small series, all requiring further evaluation in randomized controlled trials.

Keywords

Buerger's disease · Thromboangiitis obliterans · Endarteritis · Tobacco

Introduction

Buerger's disease, known also as thromboangiitis obliterans (TAO), is an inflammatory segmental obliterative non-atherosclerotic disease of medium to small arteries, superficial veins, and, less frequently, nerves. The pathological changes in TAO distinguish it significantly from systemic vasculitis. Unlike other vasculitis forms, where the blood vessel wall undergoes severe inflammation, TAO mainly features a cellular and inflammatory thrombus with predominance of polymorphonuclear leukocytes potentially forming microabscesses with minimal wall involvement. This characteristic persists across all three phases of the disease—acute, subacute, and chronic—with each stage presenting a different extent of thrombus development and inflammation. The disease occurs predominantly in young males (77%) and cigarette smokers, and the lower extremities are the main target of vascular occlusions [1].

The typical presenting symptoms are of distal extremity ischemia, ischemic ulcers, or gangrene [2]. Smoking, which is generally accepted as a risk factor for this occlusive arterial disease, may alter the immune response and increase the susceptibility to autoimmune diseases [3]; thus, complete cessation of smoking remains the cornerstone of therapy. The prevalence of the disease seems to have declined in North America over the last 30 years, probably attributed to the decline in smoking. The disease is more prevalent in the Mediterranean area, in the Middle East, Asia, and Eastern Europe.

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Table 20.1 Typical presenting signs and symptoms of thromboangiitis obliterans

Rest pain	81%
Ischemic ulcers	76%
Sensory findings	69%
Intermittent claudication	63%
Abnormal Allen test	63%
Lower extremity	50–80%
Raynaud's phenomenon	40–50%
Thrombophlebitis	40–60%
Upper extremity	10–50%
Upper and lower extremity	30–40%
Joint manifestations	12.5%

Adapted from [2, 4, 5]

Signs and Symptoms

Ischemic rest pain and ulceration of the forefoot are the typical presenting signs of the disease, and in contrast to atherosclerosis, upper extremity involvement is quite frequent [2]. Patients may present with foot and arch claudication, often misdiagnosed as an orthopedic problem, leading to a delay in the diagnosis. Multiple limbs are frequently involved; thus, it has been suggested to perform an arteriogram of both upper and lower limbs, even if the patient presents with only a single-limb involvement. Table 20.1 summarizes the typical presenting signs and symptoms of TAO. The disease usually begins with the involvement of the distal small arteries and veins and with time progresses to involve more proximal arteries. Large artery involvement is rare as a sole vascular involvement, and if existent, it usually occurs in association with small vessel disease. Multiple organ involvement in TAO is extremely rare, having been described in only single case reports. TAO patients may also present with Raynaud's phenomenon, as well as with superficial migratory thrombophlebitis, in as much as half of the cases. Arthralgias and arthritis have also been described, even as the initial presenting manifestation [4, 6].

Laboratory Findings and Serological Markers

There are no specific laboratory or radiological investigations helping in the diagnosis of Buerger's disease. The diagnosis is therefore established on the basis of investigations and tests aiming to eliminate other diseases that may mimic or simulate TAO.

The initial diagnostic workup includes various studies in order to exclude these conditions. Arteriosclerosis as well as a proximal embolic source should be ruled out as the main differential diagnostic diseases using both an arteriogram and an echocardiography. Although the arteriogram may be suggestive of TAO, there are no pathognomonic angiographic features in Buerger's disease. Generally, the proximal arteries should be normal, both in the lower and upper limbs, with no signs of atherosclerosis, aneurysmal disease, or other source of proximal emboli. The pathology, if present, is usually segmental and limited to the distal circulation (infrapopliteal and distal to the brachial artery). Typically, medium- and small-sized vessels demonstrate tapering occlusion with collaterals with a "corkscrew" and "tree root-like" configuration. These changes might be seen on the digital arteries of the fingers and toes, the tibial, peroneal, radial, and ulnar arteries; thus, segmental arterial Doppler pressures might be of some help. Basic laboratory studies include a complete blood count, liver and renal function tests, fasting blood sugar, and a lipid profile.

Patients should be screened for necrotizing arteritis with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), antinuclear antibody (ANA), complement measurements, antineutrophil cytoplasm antibody (ANCA), cryoglobulins, and scleroderma-specific antibodies, which would also help in ruling out other rheumatic diseases such as systemic lupus erythematosus, rheumatoid arthritis with vasculitis, and scleroderma. Hand radiographs might be of some help in excluding scleroderma calcinosis and a toxicological screen for cannabis and cocaine should be also included in the diagnostic workup. Thrombophilia including hyperhomocysteinemia and antiphospholipid antibody syndrome should also be looked for in these patients.

The putative role of autoimmune- and immune-mediated mechanisms in the pathogenesis of TAO was reviewed several years ago [5]. No autoantigen has been clearly identified to date in TAO. As previously stated, the disease carries an extremely strong association with tobacco use, suggesting that tobacco might be one of the environmental factors implicated in its pathogenesis. Several studies, performed many years ago, investigated both the humoral and cellular immunity, as well as HLA associations in a group of TAO patients. They claimed that while the counts of B and T cells were determined to be within normal limits, a substantial distinction was noticed in the serum levels of various cytokines in TAO patients. These include significantly higher levels of pro-inflammatory cytokines like TNF-α, IL-1, and IL-6, alongside cytokines of cellular and humoral immunity. There have been reports of high serum levels of IL-17, -22, -23, and -33, and low IL-10 in TAO patients compared to smoker controls [7]. ANA, RF, and smooth muscle antibodies were all not found in their patients. The authors did, however, detect circulating antibodies to heat-denatured human collagen (ACA) in 35% of the patients, and in none of the controls. All but one of the patients with these antibodies were smokers. None of the patients with arteriosclerosis were positive for these antibodies. These studies were taken a further step by another group who demonstrated significantly higher levels of all serum immunoglobulins, as compared with a control group, as well as the presence of specific anti-human arterial antibodies, which were found in all TAO patients, compared with only 5 of the 15 controls. The authors thus suggested that the angiitis or vascular damage seen in Buerger's disease may be due to an autoimmune process. The Tel-Hashomer group later confirmed the initial results demonstrated by others, when significant titers of anticollagen antibodies were shown to be present in 17 of 39 patients with TAO compared with none in the controls [3]. These findings were further pursued by a group of investigators who were able to demonstrate anticollagen antibodies against type I, IV, and V collagen, mainly in the subgroup of an active or severe form of the disease, as compared with healthy controls. Other investigators were able to confirm the presence of circulating immune complexes (CICs) by various techniques and even to distinguish TAO from atherosclerotic patients and normal controls by the mean values of the CICs. A search for autoantibodies in Buerger's disease found 55–60% of the patients to be positive for ANCA. Antimyeloperoxidase, antilactoferin, and antielastase autoantibodies were only found in the severe TAO group. Other studies were unable to confirm these findings. High titers of antiendothelial cell antibodies (AECA) were found in a small group of active TAO, compared with controls and patients in remission [8]. These AECAs have been recently found to be of great importance in other vasculitides such as Kawasaki disease, in which immune-mediated vascular injury and endothelial damage are present.

Preliminary studies have looked at antiphospholipid antibodies, which are also closely related to arterial and venous thrombosis. These studies found heightened levels of anti-cardiolipin and anti-Beta2 glycoprotein antibodies in individuals with TAO. Furthermore, patients exhibiting high anti-cardiolipin titers tend to be younger and face a significantly increased risk of major amputations.

The role of cell-mediated immunity against tobacco antigen in TAO patients was also investigated. In this study, the authors suggested that the relation between smoking and angiitis in TAO has to do with the modulation of the immune homeostasis via the tobacco.

The Tel-Hashomer group was also able to demonstrate the presence of cellular sensitivity to human type I and/or type III collagen in the peripheral blood lymphocytes of 77% of TAO patients, compared with much lower values in healthy male controls and in patients with atherosclerosis [3, 9].

A recent study examined histological specimens of TAO patients as well as immunophenotyping of these arteries [10]. Histology of the arteries clearly demonstrated a cellular infiltrate in the intima with thrombi, with an intact elastic lamina, as opposed to giant cell arteritis. The authors thus concluded that TAO is a vasculitis induced by an antigen in the intimal layer. Most of the infiltrating cells in the intima were CD3+ T cells.

HLA associations were also studied in Buerger's disease. The studies are mostly small and thus inconclusive, though it seems that genetic factors do play a role in the pathogenesis of TAO. The differences observed in the HLA antigens may be based on the genetic variability of the studied populations, as well as due to methodological differences used in the different studies.

Based on the available data in the literature, one may conclude that TAO does not fulfill the criteria for an autoimmune disease. Immune mechanisms do seem to be involved, although they might only be of secondary importance. These mechanisms might represent an epiphenomenon consistent with the inflammatory response. Alternatively, the possibility remains that they may represent an autoimmune reaction that has yet to be elucidated.

Diagnostic Criteria

There are no universally accepted diagnostic criteria for Buerger's disease. Table 20.2 describes the various sets of diagnostic criteria which have been proposed over the years for the diagnosis of TAO. The traditional diagnostic criteria of Shionoya from Japan [11, 12] are based on the following five criteria: smoking history, onset before the age of 50 years, infrapopliteal arterial occlusive disease, either upper limb involvement or phlebitis migrans, and the absence of atherosclerotic risk factors other than smoking. A definite diagnosis of Buerger's disease can be made if all five criteria are present. Mills and Porter [2, 13] proposed a set of more rigid major criteria, which are essential, and minor diagnostic criteria based on a cohort of patients evaluated in Oregon (see Table 20.2), whereas Papa and Adar [14] suggested a set of more flexible criteria of various clinical, angiographic, histopathologic, and exclusionary criteria for the diagnosis of the disease. They later further suggested a point scoring system to help in establishing the diagnosis of Buerger's disease [15]. Olin had also proposed a set of diagnostic criteria, which are quite similar to those of Mills and Porter, though he did not differentiate between major and minor criteria.

The scoring system of Papa and Adar is described in Tables 20.3 and 20.4 [15]. This scoring system replaces the exclusionary criteria with negatively scored criteria. The objective classification of patients is an obvious advantage of this scoring system over the other sets of criteria, thus using this system, points are awarded for young age at onset, foot claudication, upper extremity involvement, superficial vein thrombosis, and vasospastic phenomena. Atypical features detract points and the resultant score classifies the diagnosis of Buerger's disease (TAO) as being of low, medium, or high probability. None of the diagnostic sets of criteria for

Table 20.2 Diagnostic criteria for Buerger's disease (TAO)—proposed over the years

Criteria	Shionoya	Olin	Papa	Mills
Age at onset of distal extremity (years)	<50	<45	<30–40	<45[a]
Ischemia				
Tobacco abuse	+	+	+	+[a]
Infrapopliteal distal/no prox. dis.	+	+	+	+
Upper limb disease	+		+	+[b]
Migratory SVT	+		+	+[b]
Raynaud's phenomenon			+	+[b]
Intermittent claudication (foot)			+	+[b]
Exclusion of				
• Proximal embolic source		+		+
• Autoimmune diseases		+		+
• Trauma and local lesions				+
• Hypercoagulable states		+	+	+
• Risk factors for atherosclerosis: – DM/HTN – Hyperlipidemia – Renal failure	+	+	+	+
Confirmed distal disease via				
• Segmental Doppler and 4 limb plethysmography		+		+
• Arteriography *or*		+	+	+
• Histopathology		+	+	(+)
Single limb involvement (negative criterion)			+	+
Female gender (negative criterion)			+	+

DM diabetes mellitus, *HTN* hypertension, *SVT* superficial vein thrombophlebitis

[a] Major criteria

[b] Minor criteria

Table 20.3 Assessment and diagnostic criteria for Buerger's disease (TAO) based on Papa et al. Point scoring system for the diagnosis of Buerger's disease (TAO)

		Points
I. Positive points		
Age of onset	<30/30–40 years	+2/+1
Foot claudication	Present/by history	+2/+1
Upper extremity	Symptomatic/asymptomatic	+2/+1
Phlebitis migrans	Present/by history only	+2/+1
Raynaud's syndrome	Present/by history only	+2/+1
Angiography; biopsy	If typical, both/either	+2/+1
II. Negative points		
Age at onset	45–50/>50 years	−1/−2
Sex/smoking	Female/nonsmoker	−1/−2
Location	Single	−1/−2
Absent pulses	Brachial/femoral	−1/−2
AS, DM, HTN, HL	Discovered after diagnosis 5–10 years/2–5 years	−1/−2

AS arteriosclerosis, *DM* diabetes mellitus, *HL* hyperlipidemia, *HTN* hypertension

Table 20.4 Assessment and diagnostic criteria for Buerger's disease (TAO) based on Papa et al. Probability of diagnosis of Buerger's disease (TAO)

Number of points	Probability of diagnosis
0–1	Diagnosis excluded
2–3	Suspected, low probability
4–5	Probable, medium probability
6 or more	Definite, high probability

Buerger's disease have been validated; however, of the 107 patients diagnosed by Papa et al. by their old criteria, the diagnosis of TAO was rejected by the point scoring system in 20 patients. Of the remaining 87 patients, the degree of certainty in the diagnosis (point scoring system versus old criteria) was lower in 31, equal in 47, and higher only in 9. The authors suggested that their point scoring system has a better ability to discriminate patients than their old previous set of criteria, thus definitely improving the specificity of the diagnosis [15].

Recent developments in the field, gathered through a Delphi consensus involving 29 international experts, have revealed discrepancies in the current diagnostic criteria utilized globally for diagnosing Buerger's disease. The consensus emphasized the agreement on the imperative role of considering a history of tobacco consumption and the presentation of discoloration in fingers or toes in the diagnostic checklist for TAO. Yet, it was found that consensus on other clinical manifestations and paraclinical investigations was below 70%. Notably, of all the criteria advanced by Shionoya, Olin, Mills, and Papa, only one—tobacco consumption—received agreement in the consensus. Furthermore, experts agreed that histology results could differentiate TAO from atherosclerosis obliterans and other types of vasculitis, underscoring the importance of incorporating these insights into the diagnostic criteria [16].

Treatment of Buerger's Disease (TAO)

Discontinuation of tobacco use is the only effective therapy for TAO. Patients can be reassured that if they are able to refrain from tobacco use in any form including nicotine patches, the disease will remit and amputation will not occur as long as critical limb ischemia in the form of tissue loss or gangrene has not occurred already [17]. Though many medical and surgical therapeutic options for TAO have been proposed, none have been uniformly successful. With an ischemic or necrotic lesion, treatment is based on modern wound care standards with surgical debridement and selected wound dressings according to the wound's stage and condition.

Other suggested medical therapies such as Verapamil and Cilostazol may be used for associated vasospasm and intermittent claudication, respectively, but have no proven role in improving the disease progression. Other questionable therapies that have been recommended in the past but have deleterious side effects and no proven efficacy included cyclophosphamide and steroids.

Intravenous administration of a prostacyclin analog (Iloprost) was more effective than oral aspirin in a randomized trial. Healing rate of ischemic lesions as well as pain relief were significantly higher in the prostacyclin group; however, this effect was not reached with oral Iloprost [18, 19]. Intravenous prostacyclin analogs were not superior to prostaglandin E1 analogs in improving ulcer healing or reducing pain.

Recent attempts to treat TAO patients with a therapeutic angiogenesis modality using vascular endothelial growth factor (VEGF) gene therapy showed great promise with a healing effect of ischemic ulcerations and healing the rest pain these patients suffer from. An alternative way to stimulate angiogenesis has been suggested using a Kirschner wire placed in the medullary canal of the tibia, a method that has also initially showed some promising results in reducing rest pain as well as promoting healing of existing ulcers. Other preliminary experimental therapies of TAO include implantation of bone marrow mononuclear cells including endothelial progenitor cells into ischemic limbs, autologous bone marrow transplantation, stem cell therapy using umbilical cord-blood-derived multipotent stem cells, and the use of intermittent pneumatic compressions of the foot and calf. Bosentan, an endothelin receptor antagonist, has led to significant improvement of necrotic lesions and enhancement of distal circulation was also noted by radiological methods. These effects were seen despite smoking continuation [20]. All these modalities require further evaluation in randomized controlled trials to confirm their beneficial effects.

Finally, surgical revascularization is rarely possible due to the nature and size of the involved vessels. Occasionally bypass surgery is considered, the results of which are generally disappointing. Sympathectomy, which used to be one of the main modes of therapy in TAO, is still used today mainly for pain control and promotion of healing, in cases which are unresponsive to best available medical therapy. If all else fails, amputation should be as distal as possible, consistent with a reasonable chance of healing.

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Behçet's Disease

21

Gerard Espinosa

Abstract

Behçet's disease (BD) is a systemic vasculitis characterized by recurrent oral and genital ulcers, and ocular inflammation, but it may also involve the joints, skin, central nervous system, and gastrointestinal tract. Although it has a worldwide distribution, it is more prevalent in the countries along the Silk Road. The etiology of the disease remains unknown.

The diagnosis is based on clinical grounds, and classification criteria proposed by the International Study Group perform well in a clinical context. However, they present two main limitations. Firstly, the exclusion of major organ involvement, such as vascular, neurologic, and gastrointestinal involvement and, secondly, the low positivity of the pathergy test in Caucasians, reducing its diagnostic value in this group. To solve these problems, in 2014, international criteria for BD were designed based on a scoring system and including vascular and neurological involvement. The treatment of BD remains largely empirical and considerable differences exist in practical approaches to treatment. The primary goals of management are symptom control, early suppression of inflammation, and prevention of end-organ damage. Regarding prognosis, the main associates of mortality in BD are major vessel pathology and neurologic involvement.

Keywords

Behçet's disease · Classification criteria · Oral ulcers · Genital ulcers · Uveitis

Behçet's disease (BD) is characterised by recurrent oral and genital ulcers and uveitis, but cutaneous, articular, neurologic, or vascular manifestations have also been observed [1].

Epidemiology

The geographical distribution of BD is distinctive. Although it has a worldwide distribution, it is more prevalent in the countries along the Silk Road, an ancient trading route between the Mediterranean and East Asia. In Turkey, the prevalence is estimated to be between 110 and 420 per 100,000, whereas that in Japan is 13–20 per 100,000, and the prevalence in the UK and USA is estimated at 1–2 per 100,000 [2]. It has only occasionally been reported in individuals of African origin.

History

One of the earliest descriptions of an illness which bears similarities to BD is found in Hippocrates' writings from ancient Greece in 450 B.C. [3]. It was not until 1871 that individual features, such as recurrent relapsing hypopyon uveitis, oral aphthae, and combined orogenital ulcerations, were described. These features were usually attributed to tuberculosis or syphilis and, in 1937, Hulusi Behçet proposed that this triple-symptom complex might be a separate disease entity [4]. Behçet saw his first patient with recurrent aphthous stomatitis, genital ulcers, erythema nodosa, and visual disturbances in 1924. In 1930, he documented his second patient, and in

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1936, his third, and proposed that these signs constituted a specific disease entity. Finally, BD was formally recognised at the International Congress of Dermatology in 1947.

Pathogenesis

The etiology of BD remains unknown, but the most widely held hypothesis of disease pathogenesis is that a profound inflammatory response is triggered by an infectious agent in a genetically susceptible host. A combination of genetics, infectious agents, immune dysregulation and inflammatory mediators, heat shock proteins, oxidative stress, lipid peroxidation, coagulation abnormalities, and environmental factors have also been implicated [5].

The most plausible environmental trigger is an infectious agent, and evidence of ongoing or previous infection with a variety of viral and bacterial agents has been sought. These include *herpes simplex virus 1*, the hepatitis viruses, and *parvovirus B19*. Potential bacterial triggers include mycobacteria, *Borrelia burgdorferi*, *Helicobacter pylori*, and a variety of streptococcal antigens. Most recently, antibodies to *Saccharomyces cerevisiae* have been proposed as a serological marker of disease, but the clinical relevance of this finding is uncertain [6].

In every population studied, the most closely associated risk factor for disease, and in some countries for disease severity, is HLA-B51. However, the biological mechanism whereby specific HLA-B alleles confer disease susceptibility remains unknown. In addition, the relative risk of disease associated with HLA-B51 varies widely in different ethnic populations, and the disease-associated alleles are present at high frequency in some populations in whom the disease is virtually unknown [7].

Clinical Manifestations

Behçet's disease is multisystemic in nature and any organ or system in the body may be affected. Signs and symptoms are illustrated in Table 21.1, but there is a considerable variation in the pattern of system involvement of BD worldwide [1]. Recurrent aphthous ulceration is the sine qua non of BD; they are painful and appear in the gingiva, tongue, and buccal and labial mucosal membranes. Genital ulcers are morphologically similar to oral ulcers but frequently heal by scarring. They usually occur on the scrotum and penis in men and on the vulva in women.

Ocular lesions occur in the uvea and retina resulting in various symptoms, including blurred vision, eye pain, photophobia, lacrimation, floaters, and periglobal hyperemia and is one of the main causes of morbidity in BD. The most typical ocular inflammation is a bilateral non-granulomatous panuveitis with retinal vasculitis. However, isolated anterior uveitis can be seen in some cases [8].

Table 21.1 Symptoms and signs of Behçet's disease

	Prevalence
Mouth ulcers	97–99%
Genital ulcers	85%
Cutaneous involvement	70–80%
Papulopustular lesions	85%
Erythema nodosum	40–60%
Pathergy reaction	40–60%
Articular involvement	30–50%
Eye involvement	30–70%
Uveitis	50%
Vascular involvement	7–50%
Subcutaneous thrombophlebitis	25%
Deep vein thrombosis	15%
Arterial occlusion/aneurysm	5-10%
Gastrointestinal involvement	1–50%
Central nervous system involvement	20%

Skin disease in the form of erythema nodosum is common, particularly in females. It usually occurs on the front of the legs and may resolve but remaining hyperpigmented areas. Other cutaneous lesions described in patients with BD are pseudofolliculitis and acneiform nodules. Synovitis, arthritis, and/or arthralgia may occur, and the joints most frequently affected are the knees, followed by the wrists, ankles, and elbows. Destructive changes rarely occur in the joints.

The concept of vasculo-Behçet has been adopted for cases in which vascular complications are present and often dominate the clinical features [9]. Venous involvement is more common and may result in both superficial thrombophlebitis and deep venous thrombosis. Arterial complications are less common than venous involvement. Like occlusive lesions, arterial aneurysms are caused by vasculitis that begins in the vasa vasorum.

Gastrointestinal manifestations, including dysphagia, epigastric pain, colicky abdominal pain, bleeding, and diarrhea, are primarily caused by mucosal ulcerations and/or perforation.

The neurological involvement in BD primarily affects the central nervous system and includes parenchymal (with pyramidal signs, hemiplegia/paresis, behavioural changes; movement disorders, such as hemichorea, hemiballismus, and hemidystonia; hypersomnia, cranial nerve palsies, and aseptic meningitis) and nonparenchymal involvement (intracranial hypertension, due to dural sinus thrombosis) [10]. Peripheral neuropathy and myopathy are rare.

Biochemical and Serological Features

Laboratory findings are nonspecific in BD. Moderate anemia and peripheral neutrophil leukocytosis are observed in some patients. Autoantibodies, such as rheumatoid factor, antinuclear antibody, antineutrophil cytoplasmic antibody, and antiphospholipid antibody, are usually negative. Importantly, nonspecific markers of inflammation, such as C-reactive protein level and erythrocyte sedimentation rate, can be normal despite active disease. HLA typing is generally not useful in a diagnostic context because of the lack of sensitivity of the association with HLA-B51 and its high frequency in the general population in the countries with high BD prevalence [2]. It was shown in different ethnic populations to have positivity ranges around 40–60% in BD.

Diagnostic Criteria

There is no specific test or histologic finding in BD. Several sets of diagnostic criteria have been suggested for BD over the years [11]. Classification criteria have been published by the International Study Group in 1990 [12] (Table 21.2). They were a consequence of the consensus among investigators and have been widely adopted to ensure that groups of patients entering into studies would be comparable. These criteria had been shown to have 95% sensitivity and 98% specificity. The main limitation of this criteria set is the exclusion of major organ involvement, such as vascular, neurologic, and gastrointestinal involvement. Low positivity of the pathergy test is another limitation of the ISG criteria set. Although the test is positive in more than 60% of Middle Eastern patients with BD, it occurs in about 15% of Korean patients and 5% of Caucasians, reducing its diagnostic value in these groups.

In 2014, international criteria for BD (ICBD) were published and included vascular and neurological involvement [13] (Table 21.3). The ICBD criteria set is based on a scoring system attributing 2 points for oral ulcer, genital ulcer, and ocular lesions; 1 point for positive pathergy test, neurologic, and vascular involvement. Patients having 4 points are classified as BD. In an international collaborative study, the ICBD criteria set demonstrated an unbiased estimate of sensitivity of 94.8%. However, the specificity (90.5%) was lower compared to ISG (98%) [11]. On the other hand, the ICBD criteria, which seem more sensitive, especially in early disease, may cause overdiagnosis and patients with spondyloarthropathic features can be mislabeled as BD [2].

Table 21.2 International study group criteria for the diagnosis of Behcet's disease

Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient, which have recurred at least three times in a 12-month period
And two of the following	
Recurrent genital ulceration	Aphthous ulceration or scarring, observed by physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions; or acneiform nodules observed by the physician in postadolescent patients not on corticosteroid treatment
Positive pathergy test	Read by physician at 24–48 h

The findings are applicable only in the absence of other clinical explanations

Table 21.3 International criteria for Behçet's disease

BD manifestations	Score assigned
Ocular lesions	2
Oral aphthosis	2
Genital aphthosis	2
Skin lesions	1
Neurological manifestations	1
Vascular manifestations	1
Positive pathergy test[a]	1

Patients are classified as having BD with scores ≥4

[a] Pathergy test is optional

There are separate efforts for the diagnosis of specific disease manifestations of BD, such as Neuro-Behçet's Disease [14] and ocular involvement [15]. These organ-specific diagnostic approaches can be helpful, especially for the diagnosis of patients presenting with only major organ involvement in daily practice.

The differential diagnosis of BD should include Reiter's syndrome, sarcoidosis, Stevens-Johnson syndrome, and inflammatory bowel disease (Crohn's disease and ulcerative colitis with extragastrointestinal involvement). Other causes of periodic fevers, such as familial Mediterranean fever or hyper IgD syndrome, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome, should be considered in children. Patients with significant neurological involvement may occasionally be misdiagnosed as having multiple sclerosis. Other chronic systemic diseases associated with recurrent aphthous ulceration include systemic lupus erythematosus and mixed connective tissue disease [16].

Prognosis

The mortality of patients with BD ranges from 0.9% during the course of a single year's follow-up to 3.9% at 10 years [17]. Kural-Seyahi et al. [18] reported the mortality and overall morbidity in a cohort of 387 patients with BD followed during 20 years. The main associates of mortality were major vessel pathology (especially pulmonary arterial aneurysm) and neurologic involvement. Mortality was specifically increased among young males and, interestingly, tended to decrease significantly over the time. However, central nervous system involvement and major vessel disease were exceptions, because they can have their onset late, up to 10 years, during the disease course.

Therapy

The main objectives of BD treatment are to relieve symptoms, control inflammation, minimize functional disability, and prevent recurrences and end-organ damage. The choice of treatment depends on the clinical presentation and the severity of the manifestations [19]. Combination drug therapy is preferred and results in a better outcome.

Mucocutaneous lesions are commonly treated with topical corticosteroids (CS). Colchicine, pentoxifylline, and thalidomide also are used for mucocutaneous lesions, but the toxicity of thalidomide limits its application. Drugs, such as azathioprine, interferon-alpha, TNF-alpha inhibitors, or apremilast, should be considered in selected cases. Joint involvement responds to nonsteroidal anti-inflammatory drugs, colchicine, and CS.

The management of ocular inflammation requires close collaboration with ophthalmologists. According to the EULAR update recommendations, any patient with BD and inflammatory eye disease affecting the posterior segment should be on a treatment regime, such as azathioprine, cyclosporine-A (CSA), interferon alpha, or monoclonal anti-TNF antibodies. Intravitreal glucocorticoid injection is an option in patients with unilateral exacerbation as an adjunct to systemic treatment.

When the central nervous system is involved, treatment most commonly consists of combination therapy with intravenous pulse CS and cyclophosphamide. CSA and tacrolimus are not advised for the treatment of central nervous system involvement due to their increased rate of neurotoxicities.

For the management of acute deep vein thrombosis in BS, CS, and Immunosuppressives, such as azathioprine, cyclophosphamide, or CSA, are recommended. Monoclonal anti-TNF antibodies could be considered in refractory patients. Anticoagulants may be added, provided the risk of bleeding in general is low and coexistent pulmonary artery aneurysms are ruled out. For the management of pulmonary artery aneurysms, high-dose CS and cyclophosphamide are recommended. Monoclonal anti-TNF antibodies should be considered in refractory cases. For patients who have or who are at high risk of major bleeding, embolisation should be preferred to open surgery.

The treatment of gastrointestinal manifestations should include CS during acute exacerbations together with disease-modifying agents such as 5-ASA or azathioprine. For those cases with severe or refractory gastrointestinal manifestations, monoclonal anti-TNF antibodies and/or thalidomide should be considered.

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22

Susac Syndrome

Manuel F. Ugarte-Gil and Gerard Espinosa

Abstract

The Susac syndrome is a microangiopathy causing small infarcts in the brain, cochlea, and retina. It is characterized by the clinical triad of acute or subacute encephalopathy, sensorineural hearing loss, and retinal branch artery occlusions. This syndrome is probably an immune-mediated endotheliopathy that affects these organs' microvasculature.

The definite diagnosis is made by the presence of the triad of brain, retinal, and vestibulocochlear involvements. If only two domains are affected, a probable diagnosis can be proposed.

Treatment of this condition includes immunosuppression with high-dose steroids and intravenous immunoglobulin, and in some cases cytotoxic drugs.

Keywords

Susac syndrome · Microangiopathy

The Susac syndrome is a microangiopathy causing small infarcts in the brain, cochlea, and retina. It is characterized by the clinical triad of acute or subacute encephalopathy, sensorineural hearing loss, and retinal branch artery occlusions.

Epidemiology

The most commonly affected demographic group is that of young women being the female: male ratio is 2.6:1, and the age at onset usually between 16 and 40 years. The Susac syndrome has been reported worldwide; however, the largest number of cases have come from North America and Europe [1, 2].

History

The first case of this syndrome was reported by Susac et al. in 1979 [3]. These authors described two women with a progressive neurologic disorder, multifocal retinal branch artery occlusion, and hearing loss.

Pathogenesis

Preliminary evidence suggests that the Susac syndrome is an autoimmune process characterized by endothelial damage and occlusion of microvessels, leading to micro-infarctions in the brain, retina, and inner ear. Antiendothelial cell antibodies (AECA) may play a role as high levels of AECA and C4d deposition in the endothelium have been found in patients with this syndrome [3]. The deposition of C4d is considered a marker of antibody-mediated microvascular

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injury, and it is characterized by fibrin deposition, endothelial cell denudement and necrosis, with a reduplication of the vascular basement membrane zone [4–6]. Furthermore, perivascular inflammations in small leptomeningeal and parenchymal arteries as well as capillary-sized vessels associated with hypertrophy of endothelial cells have been found in pathological examinations of the brain. In addition, immunohistochemical characterization of brain tissue samples have shown the presence of CD3+CD8+ and CD68+ cells, with scarce presence of CD20+ B cells. These CD8+ T cells are associated with endothelial cells apoptosis, suggesting that CD8+ T cells are linked to triggering and perpetuation of the endotheliopathy [6].

It has also been postulated that this syndrome could be associated with clotting abnormalities, since antiphospholipid antibodies and the elevation of factor VIII have been reported in some of these patients [1, 7, 8].

Clinical Manifestations

The triad of encephalopathy, inner ear involvement, and retinal artery occlusions is clinically evident at onset in only 13% of the cases. In those who eventually develop the triad, the average time between the first symptoms and triad completion is of 21 weeks [1]. Organ involvement frequencies at disease presentation are noted in Table 22.1.

Brain involvement includes encephalopathy (76%) cognitive impairment (48%), confusion (39%), emotional disturbance (15%), and personality changes (12%), among others. Of note, cognitive impairment can be subclinical [6].

Eye involvement includes visual disturbances (56%), described as any visual symptoms including blurred vision, photopsia, scintillating scotomas, visual field defects, and decreased visual acuity [1, 6]. The type of visual disturbance depends on the location and extend of the affected retina [9].

Ear involvement mainly includes hearing loss (86%), which is usually unilateral and tinnitus (29%); it can also include vertigo and nystagmus [1, 6]. Other symptoms less frequently reported are livedo racemose, livedo reticularis, arthralgia, myalgia, or even intestinal ischemia [6].

Imaging Findings

Brain Involvement

Brain magnetic resonance imaging (MRI) may differentiate the Susac syndrome from other neurological conditions. MRI abnormalities are found in three areas: white matter, especially in the *corpus callosum*, in the leptomeninges, and in grey matter. The best sequences to observe *corpus callosum* infarctions are sagittal T2 fluid attenuated inversion recovery (FLAIR) and sagittal T1. Typical lesions in central fibers with peripheral fibers sparing are described as “snowballs,” which evolve into pathognomonic central callosal “holes.” The roof of the corpus callosum is frequently affected by microinfarcts. Furthermore, vertical, radiated linear lesions resembling “spokes” and triangular, wide-based lesions from the roof of the *corpus callosum* known as “icicles” have been reported. In patients with long-tract involvement, the internal capsule shows microinfarcts in a “string of pearls” array on MRI. These lesions are best observed on diffusion-weighted imaging during acute stages and accompanied by microinfarcts in the *corpus callosum*. The combination of typical central corpus callosum lesions and “string of pearls” in the internal capsule is pathognomonic of this syndrome [6, 10]. Other findings include periventricular white matter lesions, deep gray matter lesions, brainstem and cerebellar lesions, and leptomeningeal involvement [9].

Eye Involvement

The presence of recurrent multiple branch retinal artery occlusions in the absence of intraocular inflammation is one of the main ophthalmological features in the Susac syndrome. These occlusions can be found by fundoscopy and fluorescein angiography in 95–99% of the patients [9]. In addition to these occlusions, fluorescein angiography shows arterial wall hyperfluorescence without leakage, which can occur away from the site of occlusions or in otherwise normal-appearing retinal vessels [9]. Other ophthalmic findings include focal retinal whitening, boxcar segmentation,

Table 22.1 Organ involvement frequencies at disease presentation

	Before 2013 [1]		2013–2022 [2]
	Manifestation at onset	Manifestation during disease course	Manifestation during disease course
Complete triad	31/247 (13%)	252/297 (85%)	71/159 (47.7%)
CNS involvement	165/247 (67%)	274/300 (91%)	133/151 (88.1%)
Eye involvement	99/248 (40%)	293/301 (97%)	102/151 (67.5%)
Vestibulocochlear involvement	91/248 (37%)	288/300 (96%)	118/151 (78.1%
Headache	141/182 (78%)	171/196 (87%)	101/151 (66.9%)

arteriolar narrowing, cotton wool spots, optic disc hyperemia, optic disc pallor, perivascular sheathing, peripheral capillary closure, and arterial silver wiring [5]. The presence of retinal arterio-arterial collaterals away from the optic nerve in a young patient with a history of branch retinal artery occlusion is suggestive of Susac syndrome [11]. In addition to branch retinal artery occlusions, Gass plaques, yellow refractile lesions resembling emboli, are also found in the Susac syndrome. These plaques reflect the extravasation of lipids from vessels and are located far from arteriolar bifurcations and branch retinal arterial occlusions [12]. The optical coherence tomography can show areas of thinning of the inner retina layers supplied by the retinal microvasculature, corresponding to prior occlusions, with sparing of the outer-retinal layers that are predominantly perfused from the unaffected choroidal vasculature [9, 13].

Vestibulocochlear Involvement

Sensorineural hearing loss is the main characteristic of vestibular-cochlear involvement in the Susac syndrome, and it is caused by inner ear vasculopathy. Hearing loss is frequently unilateral; however, contralateral hearing loss may follow [12].

Laboratory Findings

Despite extensive laboratory investigation, no consistent abnormalities have been found. Minor elevations of the antinuclear and antiphospholipid antibodies can be found, and they seem to be similar than in healthy people [14]. Elevation of factor VIII and von Willebrand factor antigen levels may occur. These elevations may be due to endothelial perturbation. These factors are stored in the Weibel-Palade bodies membrane bound to the endothelium and may be released during endothelial damage. Although their elevation may be due to acute phase reactants, their close association with the endothelium would be consistent with endotheliopathy [1]. Antiendothelial cell antibodies have been reported in 25% of the patients, being not sensitive enough [15].

Cerebrospinal fluid examination may show a mild pleocytosis, and proteins are usually elevated during the encephalopathic episode. Oligoclonal bands and elevated IgG index are rarely found, unlike in most cases of multiple sclerosis [9, 14].

Pathological Features

Most reports that include brain biopsy results describe small foci of necrosis (microinfarcts), as well as vascular changes (endothelial swelling, endothelial loss, and basement membrane thickening) with absence or mild perivascular inflammation. This inflammation is mainly due to T-cells and macrophages and very rare B-cells [16].

The electronic microscopy findings include endothelial cell degeneration and necrosis, basement membrane thickening and fibrosis of vessel wall, which leads to luminal narrowing or complete obliteration and capillary loss. The most prevalent change is the thickening of the capillary wall due to collagen deposition between the two basement membrane layers. This process leads to a reduction of the vascular lumen but also it could impair the exchange of oxygen and nutrients across the capillary wall, leading to damage of the surrounding tissue even before complete occlusion of the lumen occurs. This process could be accompanied by microcavitation, lipid macrophages infiltration, and gliosis around abnormal vessels [17].

Diagnosis

The diagnostic criteria proposed but the European Susac Consortium for the Susac Syndrome includes brain, retinal, and vestibulocochlear involvement. To have a definite diagnosis of Susac syndrome, the patient should meet each criterion with its subcriteria; for the probable Susac syndrome, the patient should have two of the three listed criteria (Table 22.2) [14].

Table 22.2 Diagnostic criteria of the European Susac Consortium for Susac syndrome

Domain	Subdomain	Requirement for fulfillment of the criteria
Brain involvement	(a) Symptoms and clinical findings: new cognitive impairment and/or behavioral changes and/or new focal neurological symptoms and/or new headache (b) Imaging: Typical finding on cranial MRI: hyperintense, multifocal, round small lesions, at least one of them in the corpus callosum (“snowball”) in T2 (or FLAIR)-weighted sequences	At least one of the clinical findings and the typical MRI findings
Retinal involvement	(a) Symptoms and clinical findings: not required (b) Ophthalmological examination: BRAOs or AWH in fluorescein angiography or retinal branch ischemia in fundoscopy or corresponding damage in SD-OCT has to be documented	At least one BRAO or AWH in fluorescein angiography or retinal branch ischemia in fundoscopy or corresponding damage in SD-OCT has to be documented

(continued)

Table 22.2 (continued)

Domain	Subdomain	Requirement for fulfillment of the criteria
Vestibulocochlear involvement	(a) Symptoms and clinical findings: new tinnitus and/or peripheral vertigo (b) Examination of inner ear function: hearing loss must be supported by an audiogram and vestibular vertigo must be supported by specific diagnosis	At least one clinical finding must be present and hearing loss or vestibular vertigo must be supported by specific investigation of the inner ear function

MRI magnetic resonance imaging, *FLAIR* fluid-attenuated inversion recovery, *BRAOs* branch retinal artery occlusions, *AWH* arterial wall hyperfluorescence, *SD-OCT* spectral domain optical coherence tomography

Prognosis

Three major clinical courses have been described in patients with Susac syndrome: monocyclic, polycyclic, and chronic continuous, with an active period lasting no more than two years being the critical parameter that separates the monocyclic course from the polycyclic and chronic-continuous forms [18] The majority of the patients (54%) had monocyclic disease, 42% had a polycyclic disease, and only 4% had the chronic-continuous form [1]. However, independent of which of these courses the disease has, patients frequently have sequelae. Cognitive impairment is reported in up to 50% of patients [12]. Ophthalmic sequelae are reported in 27.5% (mainly, mild visual loss) [1]. Inner ear sequelae are reported in 89.7% (uni- or bilateral hearing loss).

Although the Susac syndrome is thought to be self-limited, late relapses may occur, especially in the retina. Mortality has been rarely associated with this syndrome, but it can be associated with the severity of the disease or adverse events associated with therapy [2].

Treatment

No clinical trials have been performed for the treatment of the Susac syndrome, but strong immunosuppressive therapy has been postulated for this condition. During the first week, the use of high dose steroids (i.e., three to seven pulses of intravenous methylprednisolone followed by high-dose oral prednisone) is recommended. Intravenous immunoglobulins (2 g/kg) are also recommended during the first week, and then given monthly at the same or lower dose for a total of 6–12 months [6, 9]. Immunosuppressive drugs (i.e., cyclophosphamide, rituximab, mycophenolate mofetil, and tacrolimus) can also be used [6]. Anticoagulation therapy could be helpful, especially in patients presenting antiphospholipid antibodies [7].

Ocular neovascularization should be treated with anti-vascular endothelial growth factor, laser photocoagulation, and/ or vitreous surgery [5].

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23

Anti-Glomerular Basement Membrane Disease (Goodpasture's Syndrome)

Miquel Blasco Pelicano and Luis F. Quintana

Abstract

Anti-glomerular basement membrane disease is a rare autoimmune disorder that primarily affects the kidneys and lungs. It is characterized by the development of autoantibodies against the non-collagenous domain of the α3 chain of type IV collagen, which is a critical component of the basement membranes in the kidneys and lungs. These autoantibodies can lead to inflammation and serious damage in these organs in the short term, with approximately 90% of patients having rapidly progressive glomerulonephritis, with or without lung hemorrhage. Patients with 100% crescents on kidney biopsy who require dialysis and show kidney failure at presentation have a dismal kidney survival rate of 8% at 1 year of follow-up. This makes anti-GBM disease one of the most aggressive forms of glomerulonephritis. Treatment is based on plasma exchange, which rapidly removes the pathogenic autoantibody, together with corticosteroids and cyclophosphamide, which inhibits autoantibody production and ameliorate inflammation. Despite treatment, currently the renal prognosis of patients who require dialysis at the time of diagnosis is poor. Imlifidase, an immunoglobulin G (IgG)-specific protease that cleaves human IgG into F(ab')2 and Fc fragments, has been proposed as an alternative to plasma exchange in refractory forms of anti-GBM disease. If the promising results obtained with imlifidase are confirmed by the ongoing phase 3 trial (NCT05679401), a paradigm shift in the treatment of the disease will occur.

Keywords

Rapidly progressive glomerulonephritis · Renopulmonary syndrome · Renal vasculitis · acute kidney injury · Imlifidase

Description of the Disease

In 1958, Stanton and Tange made the first characterization of the disease. They called it Goodpasture syndrome in honor of Ernest W. Goodpasture, which first described a patient with hemoptysis and acute glomerulonephritis, as complications of a serious infection [1]. The term Goodpasture syndrome was thereafter used for decades to nominate pulmonary-renal involvement in the presence of anti-Glomerular Basement Membrane (anti-GBM) antibodies. Currently, the most appropriate term is anti-GBM disease since afterwards also atypical forms of the disease exclusively affecting the kidney or lung have been described [2].

This is an autoimmune disorder with the target antigen present within glomerular and alveolar basement membrane, leading to rapidly progressive glomerulonephritis and alveolar hemorrhage. The noncollagenous domain of the α3 chain of type IV collagen, α3(IV)NC1, contains the main target autoantigen in this disease. Epitope mapping studies of α3(IV)NC1 have identified several nephritogenic epitopes and critical residues that bind to autoantibodies and trigger anti-GBM disease. In addition, both epitope spreading and mimicry have been implicated in the pathogenesis of anti-GBM disease, worsening disease progression [3].

It is rare life-threatening small-vessel vasculitis with an incidence of about 1 per million population per year and accounts for 15% of various causes of crescentic glomerulonephritis. Among European and Asian populations, the inci-

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dence of anti-GBM disease is estimated to be between 0.5 and 1.8 cases per million population per year [4]. In America, the prevalence of anti-GBM disease is 10 cases per million hospitalized patients [5], while it seems ultrarare in African individuals. Age distribution is bimodal, with a peak incidence in the third decade, and in the six decade, when it affects mainly females. Patients younger than 30 years more frequently present with lung involvement, while patients older than 50 years are more likely to present with isolated renal involvement [6].

At kidney biopsy, diffuse crescentic and/or necrotizing glomerulonephritis is the most frequent finding, 95% of patients will have evidence of crescent formation, and that in 80% of patients more than 50% of glomeruli will be affected [7]. Moreover, various degrees of intracapillary proliferation or interstitial inflammation may be present. Intraglomerular inflammation can finally lead to Bowman capsule rupture, an irreversible damage that may have prognostically unfavorable impact [7]. In advanced stages, the inflammatory lesions may evolve to fibrous crescents, glomerulosclerosis, interstitial fibrosis, and/or tubular atrophy [6]. At immunofluorescence, bright linear deposits of IgG1 and IgG3 (rarely IgG4 or IgA) and C3 are specifically indicative of this entity. No electron-dense deposits are detected at electron microscopy. Lung biopsy is not routinely used in the diagnosis of anti-GBM disease. If performed, linear deposits of IgG along the ABM may be observed, even if immunofluorescence on lung tissue is usually not clinically useful [6].

Clinical Findings

The presentation is abrupt and severe, with approximately 90% of patients having rapidly progressive glomerulonephritis, with or without lung hemorrhage. A characteristic feature of alveolar bleeding is the presence of hemosiderin-laden macrophages in the bronchoalveolar lavage [6]. In anti-GBM disease, recurrence is uncommon.

Patients with 100% crescents on kidney biopsy who require dialysis and show kidney failure at presentation have a dismal kidney survival rate of 8% at 1 year of follow-up. This makes anti-GBM disease one of the most aggressive forms of glomerulonephritis [8].

Laboratory Findings and Serological Markers

Serum anti-GBM antibodies are detected in approximately 90% of patients. Circulating anti-GBM antibodies are pathogenic and directly associated with disease severity. Rare cases of disease recurrence, before and after a kidney transplant, that correlated with circulating anti-GBM antibodies, have been reported.

Diagnostic Criteria

The diagnostic of anti-GBM disease relies on the demonstration of anti-GBM in tissues or circulation in conjunction with the presence of glomerulonephritis and/or alveolar hemorrhage (see Table 23.1 and 23.2). There is a huge variation in severity of both renal and pulmonary engagement in anti-GBM disease. The diagnosis can be made also in patients with mild disease in both organs, although this is unusual in clinical practice and correspond with pattern of atypical anti-GBM disease [6, 10, 13].

It is still not clear whether these milder cases represent a less frequent phenotypic expression of a disease with a wide spectrum of severity or a distinct clinical sub-phenotype determined by a different pathogenesis [8].

There are differences in antigen specificity, Ig subclass, and/or ability to recruit inflammatory cells that may account for the milder disease phenotype [14].

The discrepancy between positive linear staining for IgG in kidney biopsy and negative anti-GBM antibodies may be explained by the fact that in "atypical" anti-GBM disease

Table 23.1 Table of signs and symptoms

Typical anti-GBM disease (90% cases)	Atypical anti-GBM disease (10% cases)
80–90%: rapidly progressive glomerulonephritis: hematuria, subnephrotic proteinuria, and AKI 3 (oliguria)	Mild kidney injury (AKI 1–2) slower onset nephritic syndrome
40–60%: concurrent lung hemorrhage: hemoptysis and various degrees of dyspnea. A small minority of patients may present with isolated pulmonary disease Lung involvement should be suspected even in the absence of hemoptysis if severe anemia is present	Lung hemorrhage: rare, except in IgG4-dominant form [9]
Poor kidney outcome	Better short-term kidney outcome
References [6, 8, 10]	References [11–14]

Table 23.2 Table of laboratory findings

Typical anti-GBM disease (90% cases)	Atypical anti-GBM disease (10% cases)
Immunofluorescence: linear deposits of	IgG1 and IgG3 and C3 along GBM
LM: Diffuse crescentic necrotizing glomerulonephritis (90%)	LM: Diverse patterns predominantly focal crescentic necrotizing glomerulonephritis
Serology: IgG anti-GBM antibodies positive	Serology: IgG anti-GBM antibodies negative
Antigen: Goodpasture Ag NC1 domain of alpha 3 chain of type IV collagen	Antigen: Variable NC1 domain of all alpha chains of type IV collagen. Other GBM Ags: Entactin, Fibronectin
Antibody; IgG1-G4/G3 co-dominant, almost always polyclonal	Antibody IgG1-IgG4 codominant-IgG4. Sometimes monoclonal IgG
References [6, 10, 12, 13]	References [6, 10, 12, 13]

Table 23.3 Table of anti-GBM disease association with other autoimmune diseases

Disease	Clinical profile	How common is the association?	Clinical outcome impact	References
ANCA-associated vasculitis (AAV)	GPA and MPA Similar to anti-GBM disease	10–50 anti-GBM patients also test positively for ANCA (usually anti-MPO) 10% ANCA+ also have circulating anti-GBM antibodies	Mortality and renal survival similar to that of anti-GBM disease, multiorgan damage and relapse are comparable to AAV	[13, 16]
Primary membranous nephropathy	Anti-GBM levels were lower and serum anti-PLA2R were absent	Several cases One series of 8 patients with combined anti-GBM disease and MN	Patients had better kidney function and survival at one year, compared to the typical anti-GBM disease	[13]
Alport syndrome	Immune system of these patients is accustomed to a defective form of α3, α4, or α5 chains. The normal antigens of the kidney allograft cause an alloimmune response with the development of anti-GBM antibodies	5–10% of kidney transplants in patients with Alport syndrome	Development of overt GN is infrequent. If GN develops: higher risk of graft loss. Repeated RT :more aggressive recurrence and rapid graft loss	[13, 17]

autoantibodies may be directed against epitopes different from the common epitopes present in commercial immunoassays [15].

In routine diagnostics, the alpha-3(IV) NC is utilized as substrate by various immunoassay formats, most notably enzyme-linked immunoassay (ELISA) and indirect immunofluorescence tests, to detect anti-GBM antibodies [10]. The detection of anti-GBM antibodies in serum using ELISA with the specificity of the antibody eventually confirmed by Western blot is the preferred technique. The sensitivity of ELISA varies depending upon the commercial kit used, ranging from 63 to 100% [13]. False negative results may occur, as in the case of low antibody titers or in the presence of different immunoglobulins subclasses (as IgA or IgG4) and/or antibodies targeting antigens different from alpha-3 (IV) NC [10–13]. Falsepositive may result with commercial ELISA assays that do not use purified Goodpasture antigen. Recently, chemiluminescence immunoassay (ChLIA) has been proposed as a promising alternative tool for accurate anti-GBM antibodies (IgG) assessment since it demonstrated sensitivity of 100% at a specificity of 98.6%. Moreover, it is a reliable and efficient fully automated process [13].

Relevant Clinical Settings Associated with Anti-GBM Disease

The most frequent associations of anti-GBM disease with other clinical entities are described in Table 23.3.

Alemtuzumab is a humanized monoclonal antibody directed against the cell surface antigen CD52, used for the treatment of relapsing multiple sclerosis [8, 10]. Few cases of anti-GBM disease during the lymphocytes' repopulation phase have been described [18].

De novo anti-GBM disease in pregnancy is rare and just few cases have been described [13].

Therapy and Prognosis

Treatment is based on plasma exchange, which rapidly removes the pathogenic autoantibody, together with corticosteroids and cyclophosphamide, which inhibits autoantibody production and ameliorate inflammation; this therapeutic approach is indicated as a first line in all the individuals affected except in those who are treated with dialysis at presentation, have 100% crescents, and more than 50% global glomerulosclerosis in an adequate biopsy sample, and do not have pulmonary hemorrhage [6].

Immunoadsorption is an alternative to plasma exchange, although it may still be considered an investigational therapy [13].

There are several case reports on anti-GBM disease in which Rituximab has been used as either "add-on" to standard therapy or as a substitute for cyclophosphamide [6, 13]. Rituximab demonstrated a rapid reduction of anti-GBM antibodies, but without benefits on renal outcomes [13].

Imlifidase is an immunoglobulin G (IgG)-specific protease that cleaves human IgG into F(ab')2 and Fc fragments, causing a rapid decrease in antibody level and inhibiting antibody- and complement-dependent cytotoxicity [9, 19]. Imlifidase has been proposed as an alternative to plasma exchange in refractory forms of anti-GBM disease. In an experimental model, imlifidase was able to reduce both circulating and deposited antibodies. In particular, it was able to remove the Fc portion of the antibodies attached to the GBM, preventing complement activation [19].

In an open-label phase 2a study on 15 patients with anti-GBM antibodies, a rapid and complete clearance of anti-GBM antibodies after imlifidase infusion (add -on to standard therapy) was observed. In this study, also an improvement of renal outcomes was achieved, with 67% of patients being dialysis-independent at 6 months [9, 19]. If the promising results obtained with imlifidase are confirmed by the ongoing phase 3 trial (ClinicalTrials.gov Identifier: NCT05679401), a paradigm shift in the treatment of the disease will occur.

Currently, if the patients are promptly treated with the combination of plasma exchange, cyclophosphamide, and corticosteroids, the survival at 1 year is 80–90% and the efficacy of lung hemorrhage treatment is greater than 90% [13]. Renal survival is strictly related to the degree of kidney involvement at presentation. In patients with initial creatinine values less than 5.65 mg/dL, renal survival was 95% and 94% at 1 and 5 years, respectively. In those with creatinine greater than 5.65 mg/dL, but not requiring immediate dialysis, renal survival was 82% and 50 at 1 and 5 years, respectively. In patients requiring immediately dialysis, renal recovery occurred in only 8% at 1 year [10, 13].

Renal survival may be accurately predicted using a model with need for renal replacement therapy and the proportion of normal glomeruli as predictors [13].

In anti-GBM disease relapse is rare, occurring in <3% of patients, and is usually associated to ongoing exposure to pulmonary irritants, such as cigarette smoke and hydrocarbons exposure. There are no guidelines for the treatment of relapses, but discontinuation of environmental exposure is mandatory [6, 13].

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Kawasaki Disease

24

Jordi Antón

Abstract

Kawasaki disease is an acute systemic vasculitis of still unknown etiology. Diagnosis is based on clinical criteria that include fever, exanthema, conjunctivitis, changes in the extremities, erythema of oral mucosa and lips, and cervical lymphadenopathy. However, these criteria have low sensitivity and specificity, and therefore, other clinical and laboratory features may be helpful in establishing the diagnosis, especially for cases of atypical or incomplete Kawasaki disease. Prognosis depends on the extent of cardiac involvement; developing coronary aneurysms 20–25% of untreated patients, which may lead to myocardial infarction and sudden death. Treatment with high-dose intravenous immunoglobulin is effective in reducing the risk of coronary aneurysms in most cases. Corticosteroids are considered for refractory cases and in the initial treatment in patients with higher risk. Multisystem Inflammatory Syndrome in Children (MISC-C), a rare postinfectious hyperinflammatory disorder associated with SARS-CoV-2, and with features overlapping with Kawasaki disease has been identified in last years.

Kawasaki disease (KD) is a systemic vasculitis that affects small and medium-sized vessels [1]. It is an inflammatory process, self-limited, but potentially life-threatening depending on the extent of cardiac involvement. The disease was first described by Tomisaku Kawasaki in 1967, in 50 children with a mucocutaneous lymph node syndrome, with high fever and a characteristic desquamation of fingers and toes [2].

Epidemiology

Even though KD is markedly more prevalent in Asiatic countries, it has a universal distribution and can be manifested in any race and ethnic group. It is a pediatric disease, and in most of the series, 85% of patients are less than 5 years old. KD is more common in boys (male/female ratio 1.5–2.1/1).

Pathogenesis

The etiology of KD is still unknown, although clinical, laboratory, and epidemiological features suggest an infectious origin. However, multiple studies have failed to identify a unique infectious agent in KD. Nor has been it proved to be related to exposure to any drug or as a response to a superantigen. Genetic factors also play a role, as the disease is more prevalent among certain ethnic groups and family history increases risk; moreover, genome-wide association studies have implicated single-nucleotide polymorphisms in different genes. On the other hand, activation of innate immune system is an evident characteristic of KD, with activation of proinflammatory cytokines pathways (IL-1, IL-6, TNF). A reasonable hypothesis is that KD is an inappropriate and exaggerated immune response to one or multiple environmental or infectious agents that elicits the disease in a genetically susceptible individual. The self-limited nature of the disease and the low rate of recurrence suggest an adaptative immune response that protects against future encounters with the KD gent.

Clinical Manifestations (Percentages of Appearance Enclosed in Brackets) [3, 4]

Fever (100%): The fever in KD is typically high-spiking and remittent (in many cases >40 °C). It is often resistant to antipyretics.

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Changes in extremities (93%): Erythema and edema of hands and feet, which is sometimes painful, is a frequent manifestation of KD at the beginning of the disease and lasts 1–3 days. Desquamation of fingers and toes appears in the convalescence phase (2–3 weeks after fever onset), and therefore is useful only to confirm the diagnosis, but not to decide when to start treatment. A subtle perineal desquamation may also be observed earlier in the disease. Approximately 1 or 2 months after the onset of fever, small transverse grooves across fingernails can appear (Beau's lines).

Exanthema (95%): The exanthema in KD is polymorphous and nonspecific. It is often an erythematous, maculopapular rash; but occasionally can appear other rashes, such as scarlatiniform, micropustular, and erythroderma. It has not been described a bullous or vesicular eruption. It can be seen in the acute phase of illness, often during the first 5 days of fever. The exanthema is usually extensive; affecting predominantly the trunk, but it can also be limited to the perineal region.

Conjunctival injection (90%): The conjunctivitis is bilateral, painless, and non-purulent, affecting the bulbar conjunctiva (sparing the limbus). It usually begins shortly after the onset of fever and is transient (sometimes can only be seen during 1 day in the acute phase of the illness). A mild acute iridocyclitis or anterior uveitis may also be noted by slit lamp) [4].

Changes in lips and oral cavity (93%): The lips are dry, cracked, with hemorrhagic erythema; there is a characteristic strawberry tongue with prominent papilla; and a diffuse erythema of oropharyngeal mucosal surfaces. Ulcers and pharyngeal exudates are not suggestive of KD.

Cervical limphadenopathy (43%): It is usually unilateral and confined to the anterior cervical triangle. There must be at least one adenopathy ≥1.5 cm in diameter (to fulfill diagnostic criteria), although using cervical ultrasound, multiple adjacent enlarged nodes may be detected.

Other clinical findings: Clinical findings other than the classical diagnostic criteria are common in KD and may help us making the diagnosis. Gastrointestinal manifestations are present in approximately one-third of the patients, including vomiting, diarrhea, and abdominal pain. Gallbladder distention (hydrops) can also occur in KD [5]; and in some patients liver enlargement and jaundice have been reported.

Characteristically, patients with KD have marked irritability, to the point that if it is not present, other diagnosis should be considered. This may reflect aseptic meningitis that is found in those KD patients that a lumbar puncture is performed. Transient sensorineural hearing loss and facial paralysis are rarely present [6].

Arthritis and arthralgia may also be observed during the acute phase or convalescence, affecting both small and large joints. Induration and erythema at the site of a previous vaccination with Bacille Calmatte-Guérin has also been described [7].

Cardiac manifestations, such as myocarditis and pericarditis, occur in the acute phase of illness, whereas coronary aneurisms are formed in later stages.

Laboratory Findings

A specific laboratory test for the diagnosis of KD does not exist. However, some investigations can be performed to help with the diagnosis.

Blood test may show leukocytosis and elevated acute phase reactants—C reactive protein, erythrocyte sedimentation rate—and normocytic normochromic anemia. Thrombocytosis (which can be over 1 million/mm^3) typically develops in the second or third week of disease. Other findings include elevated liver enzymes, lipid profile alterations (decrease in high-density lipoprotein (HDL), cholesterol levels, and increase in triglycerides), hypoalbuminemia, hyponatremia, and more rarely, hyperbilirubinemia.

Urinalysis may reveal sterile pyuria, while in cerebrospinal fluid evidence of aseptic meningitis with pleocytosis and normal glucose and protein levels can be seen.

Echocardiography

In the acute phase of illness, an echocardiographic evaluation may reveal signs of myocarditis with decreased ejection fraction; pericarditis, mitral regurgitation, and perivascular brightness of the coronary wall. Coronary aneurysms generally appear in the convalescence phase (from second week). Ideally, echocardiography should be performed at least at diagnosis, at week 2 and between week 6 and week 8 of illness [4].

Course of the disease. The course of KD can be divided in three phases [8]:

- *Acute febrile phase (1st–2nd week):* KD appears suddenly, with high fever and irritability, and progressively other symptoms are added: adenitis, conjunctivitis, erythema and edema of hands and feet, changes in oral mucosa. If untreated, these symptoms stay for 12–15 days and then disappear. Common analytical findings in this stage are leukocytosis and increase in acute phase reactants, with normal or slightly low hemoglobin and normal platelets.

– *Subacute phase (3rd–6th week):* Once the patient has been treated with immunoglobulin, fever disappears, symptoms return to normal and a typical periungual desquamation of finger and toes is usually seen. Laboratory tests may show marked thrombocytosis and anemia, with normalization of leukocytosis and acute phase reactants. It is in this phase that coronary aneurysms develop.
– *Convalescence phase:* Most of the patients are asymptomatic at this stage, although Beau lines may be observed in fingernails. Blood tests return to normal and coronary aneurysm can disappear or not, and they may become symptomatic in the form of myocardial infarction.

Table 24.1 Diagnostic criteria for Kawasaki disease

Fever of ≥5 days[a] and presence of ≥4 principal features[b]
1. Changes in extremities
(a) Acute phase: erythema of palms and soles; edema of hands and feet
(b) Subacute phase: desquamation of fingers and toes
2. Polymorphous exanthema
3. Bilateral bulbar conjunctival injection
4. Changes in lips and oral mucosa: erythematous and cracked lips, strawberry tongue, and oral and pharyngeal hyperemia
5. Cervical lymphadenopathy (>1.5 cm diameter)
Exclusion of other diseases with similar findings[c]

[a] Patients with at least 5 days of fever and <4 principal criteria can be diagnosed with KD when coronary artery abnormalities are detected

[b] In the presence of ≥4 principal criteria, KD diagnosis can be made on day 4 of illness, or even before by experienced clinicians who have treated many KD

[c] See Table 24.2

Diagnostic Criteria

Clinical criteria are used to diagnose KD. More extended criteria are based on the presence of at least 5 days of fever and at least 4 of the 5 principal clinical features (Table 24.1) [4].

Incomplete (Atypical) KD

Regardless of how the diagnostic criteria are applied, they have both low sensitivity and specificity. Some patients with suspected KD do not fulfill the diagnostic criteria, and diagnosis is made based on compatible laboratory and/or typical echocardiographic findings.

Children under one year of age, and especially those younger than 6 months, are more frequently affected with an incomplete form of KD, and therefore, it is important that a correct diagnosis is made, and early treatment started in these patients, because in addition, they are at higher risk of developing coronary aneurysms, shock at diagnosis and admissions in ICU, than older children. In such cases, clinicians should pay attention to other clinical or laboratory findings not included in the diagnostic criteria that are useful in corroborating the diagnosis [9].

Differential Diagnosis

Because KD has unspecific symptoms that are like those in other diseases, a precise differential diagnosis is required, in order to carry out an adequate treatment and not to underdiagnose nor overdiagnose—especially in incomplete KD cases. Diseases with similar clinical features are reflected in Table 24.2.

Table 24.2 Differential diagnosis of KD

Infectious diseases	Viral (adenovirus, measles, enterovirus, rubella, parvovirus B-19, herpesvirus 6, Epstein-Barr virus) Multisystem inflammatory syndrome in children (post-Covid-19) Bacterial (scarlet fever, acute rheumatic fever, Rocky mountain spotted fever, leptospirosis, tularemia, bartonellosis) Mycoplasma pneumoniae
Toxin-mediated	Staphylococcal scalded skin syndrome Toxic shock syndrome
Rheumatic diseases	Systemic juvenile idiopathic arthritis (Still's disease) Polyarteritis nodosa Systemic lupus erythematosus Reactive arthritis Autoinflammatory diseases
Hypersensitivity reactions	Drug hypersensitivity reactions Steven-Johnson syndrome
Toxicity	Acrodynia (mercury poisoning)

Treatment

Although the exact mechanism of action is unclear, effective therapy exists for the majority of patients with acute KD. Treatment with intravenous immunoglobulin (IVIG) has reduced the risk of developing coronary aneurysm from 20–25% to less than 5% if administered within the first 10 days of illness [4].

High-dose (80–100 mg/kg/dose) or medium-dose (30–50 mg/kg/dose) aspirin have been used in the initial treatment of KD for many years. However, they do not appear to lower the frequency of development of coronary abnormalities, duration of fever, or duration of hospitalization [10]. So, currently other less toxic nonsteroidal anti-inflammatory agents are suggested for the control of fever. Nowadays, aspirin is proposed as an antiplatelet dose (3–5 mg/kg in a single daily dose) for 6–8 weeks. Then it is discontinued if platelets count and acute phase reactants have returned to normal and there are no signs of coronary abnormalities in the echocardiography.

Treatment with IVIG should be administered early in the course of the disease, preferably within the first 10 days of illness (if possible, between day 5th and 7th). Recommended doses are 2 g/kg in an 8–12 h infusion. In patients presenting after day 10th of illness, IVIG should only be administered in those having signs of ongoing systemic inflammation (increased acute phase reactants) together with either persistent fever without other explanation or coronary artery aneurysms. Patients with persistent or recrudescent fever 36 h or more after the IVIG infusion (10–20% of patients do not respond to a single dose) can benefit of a second dose of IVIG but an adjunctive therapy must be strongly considered.

Corticosteroids use in KD were controversial, nowadays there is evidence that use of steroids in the acute phase of KD can be associated with reduced coronary artery abnormalities, reduced inflammatory markers, and shorter duration of hospital stay when compared to no corticosteroids [11]. This is of relevance especially for those populations with higher risk of coronary aneurism. Several scores have been proposed to identify children with higher risk of aneurisms, mostly in Asia, but they have not been reproducible in other populations [12]. Younger age (less than 12 months), hyponatremia (<133 mmol/L), hypoalbuminemia (<35 g/L), thrombocytopenia (<300,000/mm^3), increase in transaminases (>100 UI/L), low hematocrit (<35%), or decreasing since diagnostic, elevated PCR (>200 mg/L), coronary dilatation at diagnostic, macrophage activations syndrome and shock, have been identified as risk factor [13], and early treatment with corticosteroids is reinforced. Usually pulsed intravenous methylprednisolone (30 mg/kg per dose) followed by prednisolone (2 mg/kg/day) taper over weeks.

For those patients who still do not respond, there are other optional therapies that have been effective in some clinical trials and case series. Both TNF and IL-1 beta have been implicated in vascular endothelial cell damage and coronary artery lesions. Probably the most accepted is administered a TNF blocker, such as infliximab. Two prospective trials and case studies also reported successful use of anakinra, an IL-1 receptor antagonist, in the treatment of refractory KD [13]. Other immunosuppressive agents are reported to be effective in patients with refractory KD including calcineurin inhibitors like cyclosporine, plasma exchange, cyclophosphamide, methotrexate or rituximab [14].

Kawasaki Disease and Multisystem Inflammatory Syndrome in Children (MISC-C)

MISC-C is a new, rare postinfectious hyperinflammatory disorder associated with SARS-CoV-2. It presents about 2–6 weeks after a COVID-19 infection, and its clinical presentation and symptoms overlaps with KD. Both KD and MIS-C involve an exaggerated immune response, resulting in inflammation of blood vessels (vasculitis) and multiple organ systems.

MIS-C is being observed in older children, including adolescent, and there is no significant difference in the sex ratio. Clinically MIS-C patients presents more frequently respiratory, gastrointestinal symptoms and shock, and a lower incidence of conjunctivitis. MIS-C patients had lower lymphocyte counts, platelet counts, erythrocyte sedimentation rates, alanine transaminase, and albumin levels and had higher levels of aspartate transaminase, N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), troponin, C-reactive protein, D-dimer, fibrinogen, ferritin, and creatinine. MIS-C patients have a higher incidence of left ventricle dysfunction, valvular regurgitation, pericardial effusion, myocarditis, and pericarditis. The incidence of coronary artery lesion is lower in MIS-C patients [15]. Different criteria for helping in the diagnosis have been proposed (Table 24.3) [16].

Table 24.3 Case definition of multisystem inflammatory syndrome in children (MIS-C), according to Centers for Disease Control and Prevention (CDC), December 2022

An individual aged <21 years and in the absence of a more likely alternative diagnosis
• Subjective or documented fever (*T* > 38.0 °C)
• Clinical severity requiring hospitalization or resulting in death
• C-reactive protein (CRP) >3.0 mg/dL
• New onset manifestations of >2 of the following categories:
– Cardiac: coronary artery dilatation/aneurysm, left ventricular ejection fraction <55%, or troponin elevated above normal
– Shock
– Mucocutaneous: rash, oral mucosal inflammation, conjunctivitis/conjunctival injection or extremity findings (erythema, edema)
– Gastrointestinal: abdominal pain, vomiting, or diarrhea
– Hematologic: platelet count <150,000/μL, absolute lymphocyte count <1000/μL
• Detection of SARS-CoV-2 nucleic acid/antigen up to 60 days prior to or during hospitalization or in a postmortem specimen, or detection of antibody associated with current illness, or close contact with a confirmed/probable COVID-19 case in the 60 days prior to hospitalization

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Cogan's Syndrome

25

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Abstract

Cogan's syndrome (CS) is a rare autoimmune disorder characterized by interstitial keratitis, vestiboloauditory symptoms, and a wide spectrum of ocular inflammation. Typical (classical) and atypical variants of CS are usually defined to have different clinical combinations. Typical CS is classically presented by ocular involvement that is primarily interstitial keratitis with cochlear vestibular symptoms, such as sudden onset of nausea, vomiting, tinnitus, vertigo along with progressive hearing loss. Atypical CS is presented by scleritis, iritis, and frequently with systemic immune-mediated inflammation, such as systemic vasculitis. Treatment includes corticosteroids a first-line treatment, other immune-suppressive agents such as anti-TNF drugs. In severe and unresponsive cases, biological drugs are considered to be efficient and with a favorable outcome.

Keywords

Cogan's · Autoimmunity · Progressive hearing loss · Interstitial keratitis

Introduction

Cogan's syndrome is a rare disease, mainly occurring in young adult. Morgan and Baumgarther published the earliest description of non-syphilitic keratitis coexisting with vestibuloauditory disturbances in 1934. In 1945, the ophthalmologist David G. Cogan described four patients with the same symptoms and classified this entity as "Cogan's syndrome" (CS) [1]. Later, Cody and Williams called attention to the frequent copresence of systemic manifestations of this syndrome [2]. This led to the division of CS into typical and atypical varieties based on the type of ocular inflammation present and audiovestibular symptoms [3]. Typical CS manifests primarily with interstitial keratitis, and hearing loss, whereas atypical CS exhibits other inflammatory ocular involvement, such as iritis, episcleritis in addition to systemic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, and systemic vasculitis. Atypical CS carries usually a less favorable prognosis than typical CS [4].

The Pathogenesis of Cogan's Syndrome

Although the pathogenesis of CS remains obscure, autoimmune-mediated cellular and humoral processes have been postulated by many investigators. This opinion has been supported by the findings of antibodies against inner ear and corneal tissues along with the presence of a lymphocytic and plasma cell infiltrates in the cornea and the inner ear [5]. In this respect, anti-Hsp70 antibody positivity was especially high in typical CS (92.9%) compared to that in atypical CS (16.6%), suggesting anti-Hsp70 antibodies a serological marker for typical CS [6]. In an elegant study, Lunardi et al. found that DEP-1/CD148 is a pathogenetically relevant autoantigen target in CS. It is a widespread cell-surface antigen, which is expressed on endothelial cells, and supporting cells within the sensorineural epithelia in the inner ear as well as on nerve and glial cells. In this regard, the injection of purified antibodies to DEP-1/CD148 into Balb/c mice resulted in hearing loss [7]. Histological analysis of the inner ear showed degeneration of the sensory receptors and supporting structures of the cochlea and vestibular apparatus and demyelination and atrophy of the vestibular and cochlear branches of the eight cranial nerves [8]. Several authors have noted an upper respiratory tract infection immediately preceding in 50% of cases of CS, suggesting an infectious origin. However, surveying for infections is usually negative.

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The possible suspected infections include Chlamydia, Mycoplasma pneumoniae, Epstein-Barr virus, Herpes Simplex virus, Varicella-Zoster virus, Cytomegalovirus, and influenza A, B [9]. In a recent report, Cogan syndrome was described to develop following SARS-COV-2 infection [10]. Thus, it is suggested that CS can be triggered by vaccination and infection, which may lead in some cases to a hypersensitivity response with possible cross immunity to similar proteins in the tissues of the audiovestibular system, eye, or other organs, as well as those associated with vasculitis.

Clinical Features

In an early review by Gluth et al., the most common presenting symptom of CS was sudden hearing loss, reported in 50% of patients, followed by balance disturbance in 40%, ocular irritation in 32%, photophobia in 23%, tinnitus in 13%, and blurred vision in 10%. Interestingly, only 5% of the patients presented with both vestibuloauditory and ophthalmologic symptoms at the onset of the disease.

In this series, 47% of patients initially presented only vestibuloauditory signs while 33% only ophthalmologic symptoms. Seven percent of patients presented constitutional symptoms including myalgia, arthralgia, headache, rash, and fever at the onset of the disease. In most patients (85%), both vestibuloauditory and ophthalmologic symptoms developed in less than 2 years [11].

Ophthalmic Manifestations

The typical presentation of CS is, in most cases, the occurrence of bilateral interstitial keratitis (IK). IK tends to appear in close proximity to episodes of audiovestibular dysfunction. IK is rarely asymptomatic, and most of the patients manifest intense photophobia, lacrimation, eye pain, and disturbances in visual acuity. On examination of patients with IK, early typical findings include subepithelial peripheral corneal stromal infiltrate. Consequently, secondary neovascularization may frequently ensue.

In most cases, both eyes are affected during the disease course, with great variability in symptoms from one eye to the other, and from day to day. The ocular manifestations may have a relapsing course with periodic attacks occurring during the years. Patients are designated as having atypical CS if another significant inflammatory eye lesion in addition to, or rather than, IK is present (Table 25.1). In the atypical CS group, the main ocular manifestations are uveitis and episcleritis [12]. A moderate and usually transient decrease in visual acuity is not infrequent in CS, but amaurosis or blindness may also occur.

Table 25.1 Ocular manifestations of Cogan's syndrome

Typical	Atypical
Interstitial keratitis	Scleritis/episcleritis
Subepithelial peripher al corneal stromal	Retinal artery occlusion
Infiltrates	Choroiditis
	Retinal hemorrhage/vasculitis
	Papillitis
	Isolated conjunctivitis[a] Isolated subconjunctival hemorrhage[a] Isolated iritis[a] Uveitis

[a] Only if it is associated with Meniere-like episodes within an interval of 2 years

Audiovestibular Manifestations

In both typical and atypical CS, the classical audiovestibular presentation is sudden onset of nausea, vomiting, tinnitus, vertigo, and hearing loss, which is usually bilateral. In their review, Gluth et al. [11] reported that the most common otolaryngologic symptoms, which appeared in their patients during the disease course, included hearing loss (100%), vertigo (90%), tinnitus (80%), ataxia (53%), and oscillopsia (25%). Vestibular function tests abnormalities, such as bilateral absence of vestibular responses to caloric testing and bilateral weak vestibular responses to caloric testing, were found in most patients. Additionally, physical examination revealed spontaneous and/or gaze-induced nystagmus at some point of their disease in 20% of the patients. Usually, the hearing loss in CS is classified as sensorineural, preferentially affecting medium to high frequencies. These manifestations, along with the visual symptoms, usually occur either concurrently or sequentially within a few weeks to months. Rarely, years may separate the appearance of visual and audiovestibular manifestations. Physical examination often reveals sudden bilateral sensorineural hearing loss, tinnitus, and constant vertigo accompanied by cephalea. Despite medical treatment, hearing loss may progress to irreversible profound hearing loss in about half of CS patients resulting in the need for cochlear implantation.

Systemic Manifestations

Approximately, 70% of patients with CS have systemic diseases frequently presented with general constitutional symptoms, such as, headache, arthralgia, fever, weight loss, fatigue, arthritis and myalgia [13]. The two most serious systemic complications are vasculitis and cardiovascular involvement. Vasculitis can involve all layers of different-sized vessels. Clinically, vasculitis has been documented in the skin, kidneys, subcutaneous nodules, coronary and cerebral arteries and muscles [14]. Atypical Cogan's syndrome was reported to mimic giant cell arteritis presented with headache, temporal artery tenderness, and increased serum level of interleukin-6. Cardiovascular involvement is present in 10% of CS patients. The most characteristic cardiovascular manifestation of CS is aortitis with aortic insufficiency. Other manifestations include, aortic dilatation, aortic valvular insufficiency, congestive heart failure, pericarditis, arrhythmias, and silent coronary artery disease. Comparison of typical CS and atypical CS showed that cardiovascular manifestations were more common in atypical Cogan's syndrome. Neurologic symptoms of CS are present in approximately 50% of cases, including headaches, psychosis, coma, convulsion, neuropathy, and stroke [15].

Additionally, atypical CS has also been reported to be associated with other systemic diseases, such as sarcoidosis, rheumatoid arthritis, juvenile idiopathic arthritis, Sjögren's syndrome, Crohn's disease, ulcerative colitis, and Wagener's granulomatosis [16].

Laboratory and Radiological Data

Laboratory abnormalities have been found in CS patients but none is diagnostic.

They include an elevated erythrocyte sedimentation rate (ESR), leukocytosis with neutrophilia, anemia, and thrombocytosis. Nonspecific markers of inflammation, such as elevated C-reactive protein and high levels of gamma globulin, have also been found. Low titers of rheumatoid factor, antinuclear antibodies, and ANCA were detected in a few patients. Antibodies against the inner ear may support the diagnosis of CS. Anti-Hsp70 antibodies were suggested to be a serological marker for typical CS [6]. Some authors reported that in CT and MRI, there was evidence of narrowing or obliteration of parts of the vestibular labyrinth that are related to the risk of permanent hearing loss [17]. However, in the review by Gluth et al., both CT (14 patients) and MRI (20 patients) of the head were normal.

Treatment

Glucocorticosteroids are the primary treatment for CS. Ocular manifestations in CS may respond well to topical corticosteroids. Recently, topical cyclosporin A was successfully used in the treatment of severe anterior segment inflammation. Systemic steroids are indicated for CS as first-line treatment for ocular signs, vestibuloauditory symptoms, and particularly bilateral hearing loss. When hearing improves, steroids are tapered slowly and continued for 2–6 months. If there is no response after 2 weeks, the steroids are rapidly tapered. When symptoms are still refractory, immunosuppressive drugs, such as cyclosporine A, methotrexate, are combined. For severe unresponsive vasculitis, immunosuppressive drugs such as cyclosporin A (0.5–2 mg/kg/day) or cyclophosphamide (1.5–2.0 mg/kg/day) in conjunction with prednisone have been used successfully [18]. In cases of relapse despite therapy with corticosteroids and immunosuppressive agents, anti-TNF drugs were reported to be beneficial in improving the prognosis of CS [19]. Biological drugs, such as infliximab, rituximab, and tocilizumab, are a safe option, but results on hearing loss are awaiting larger patients' cohorts [20]. Patients with profound hearing loss after unsuccessful treatment with anti-inflammatory drugs are candidates for cochlear implantation.

Diagnostic Criteria

The diagnosis of Cogan's syndrome is mainly based on clinical issues. Unlike other systemic collagen or autoimmune diseases, it is not associated with a specific autoantibody. The laboratory profile (elevated ESR and leukocytosis) of the disease is a reflection of the extent of the inflammation and cytokine cascade and therefore no laboratory or radiographic test is diagnostic of CS. Hence, the diagnosis of Cogan's syndrome is based on clinical findings of both ocular and audiovestibular abnormalities in the setting of a negative laboratory workup for syphilis or other immune-mediated disease. When a patient presents without interstitial keratitis or the audiovestibular symptoms are not present concomitantly, the diagnosis of CS becomes highly questionable. The differential diagnosis of CS should include diseases causing an interstitial keratitis, audiovestibular diseases associated with eye findings, and systemic diseases that include ocular and ear manifestations (Table 25.2). The other difficulty in

Table 25.2 Differential diagnosis of Cogan's syndrome

Infectious
Congenital and acquired syphilis
Chlamydial infections
Mumps
Herpes zoster
Rubeola
Immune-mediated diseases
Polyarteritis nodosa
Granulomatosis with polyangiitis
Rheumatoid arthritis
Relapsing polychondritis
Temporal arteritis
Sjögren's syndrome
Behçet's disease
Sarcoidosis
Systemic lupus erythematosus
Others
Vogt-Koyanagi-Harada syndrome
Susac syndrome

gathering diagnostic criteria arises from the low incidence of reported cases of the disease. Until now, approximately 250 cases have been reported in the English literature. It can be assumed that the true frequency is higher.

In summary, typical CS type criteria should include ocular involvement that is primarily interstitial keratitis with audiovestibular involvement, which is similar to Meniere's disease (sudden onset of nausea, vomiting, tinnitus and vertigo) along with progressive hearing loss. The time interval between ocular and audiovestibular involvement may be as long as 2 years.

Atypical CS type can be diagnosed in three groups of patients. The first group includes patients with classic relapsing pattern of autoimmune-type vestibuloauditory symptoms in addition to the presentation of other types of inflammatory eye disease, with or without IK (Table 25.1). The second group includes patients with more than 2 years between the onset of the ophthalmologic symptoms and the audiovestibular manifestations. The third group includes patients with typical ocular manifestations associated, within 2 years, to audiovestibular symptoms different from Meniere-like episodes.

It seems important that primary physicians should suspect, as early as possible, the diagnosis of CS. These patients could benefit from early referral to specialized centers, where early initiation of immunosuppressive drugs could prevent permanent hearing loss and the need for cochlear implants.

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26

Immunoglobulin A Vasculitis

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Abstract

Immunoglobulin A vasculitis (IgAV), formerly known as Henoch-Schönlein purpura, is a primary immune complex vasculitis affecting small vessels, characterized by IgA1-dominant immune deposits. IgAV is the most common vasculitis in childhood, and is characterized by cutaneous lesions, being palpable purpura the most frequent initial sign, followed by joint, gastrointestinal, and renal involvement. Glomerulonephritis and gastrointestinal complications are considered severe manifestations of IgAV. Regular laboratory tests are not useful in the diagnostic process. However, new serum and urine biomarkers are emerging as prognostic factors in assessing potential organ-threatening involvement. IgAV diagnosis relies on clinical criteria supported by histopathologic findings. Classification criteria have been delineated for pediatric and adult patients. Therapeutic recommendations include glucocorticoids in patients with renal, abdominal, and other organ- or life-threatening situations. Additional immunosuppressive agents may be used in patients with severe IgAV glomerulonephritis, and glucocorticoid-resistant or refractory cases. Rituximab, an anti-CD20 monoclonal antibody, has showed promising results in patients with renal involvement and refractory situations.

Keywords

Immunoglobulin A vasculitis · IgAV · Small vessel vasculitis · IgA nephropathy · IgAN · Classification criteria · Diagnosis criteria · Rituximab

Immunoglobulin A vasculitis (IgAV), formerly known as Henoch-Schönlein purpura, is a primary immune complex-mediated vasculitis affecting small vessels (predominantly capillaries, venules, or arterioles), with IgA1-dominant immune deposits [1]. The histopathologic hallmark of IgAV is leukocytoclastic vasculitis, mainly expressed as cutaneous purpura followed by articular, gastrointestinal, and renal manifestations [1].

Epidemiology

IgAV is the most common systemic vasculitis in childhood, occurring up to 30 times more frequently than in adults, with no clear sex predominance [2–4]. Caucasians are more often affected than non-Caucasian patients. In European populations, IgAV pediatric incidence ranges between 3 and 27 cases per 100,000 inhabitants, while in adults, it is estimated between 1.5 and 14 cases per million inhabitants [2–4]. A seasonal pattern, with a predominance of cases during the autumn and winter months, has been observed in pediatric patients, but not in adults [3, 4]. A triggering factor is identified in 30–50% of patients, mainly previous infections (especially of the upper respiratory tract), drugs intake, and solid or hematologic malignancies [3–5].

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Pathogenesis

The etiology of IgAV is unknown, but environmental and genetic factors seem to influence in its pathogenesis. IgAV is characterized by inflammation of the vessel walls with IgA1-immune deposits, complement factors, and neutrophil infiltration [6]. The formation of galactose-deficient IgA1 (Gd-IgA1) and related immune complexes seems to play a crucial role in the development of IgA glomerulonephritis. In addition, neutrophil activation is stimulated through the binding of IgA to the Fc alpha receptor I expressed on its surface, resulting in systemic vascular inflammation and tissue damage [7].

Genetic studies have associated the HLA region with IgAV. In addition, a susceptibility risk locus shared between IgAV and Kawasaki disease, two pediatric diseases, has been recently identified, indicating a potential role of the lysosomal pathway in the IgAV pathogenesis [8].

Clinical Manifestations

The main clinical manifestations of IgAV are listed in Table 26.1. Cutaneous purpura, the guiding manifestation of IgAV, consists of purple spotted skin lesions, usually of 2–10 mm in diameter, mostly occurring in the lower limbs, buttocks, and less frequently in the trunk and upper extremities (Fig. 26.1). Depending on the disease severity, lesions can be higher, and even converge over large areas, and become hemorrhagic and necrotic [5]. Erythema multiforme-like lesions have been also described. It rarely affects the face and mucous membranes [5]. After the acute episode, purpuric lesions usually resolve leaving transient residual hyperpigmented lesions (Fig. 26.1).

Arthralgia occurs in about 60–85% of patients with IgAV, mainly involving the knees and ankles, and less frequently the wrists and fingers. Joint symptoms may precede purpuric lesions in some cases [4]. Arthritis has been found to occur more frequently in children than in adults [4, 9].

Gastrointestinal manifestations, which may also precede cutaneous purpura, occur in 50%–75% of pediatric patients, while in adults, this proportion seems to be higher. Among all the segments of the gastrointestinal tract, small bowel is the most commonly affected. Digestive complaints include cramping abdominal pain, vomiting, gastrointestinal bleeding, and intestinal intussusception (mainly in children) [4, 5, 9].

Renal involvement as mesangiocapillary glomerulonephritis with IgA deposits is observed in 40%–50% of patients, mainly occurring in adults and children over 8 years of age,

Table 26.1 Main manifestations in a pediatric and an adult series of patients with IgAV

Clinical manifestations	Children $n = 73$ (%)	Adults $n = 31$ (%)
Palpable purpura	**100**	**100**
Cutaneous location		
Lower extremities	100	100
Upper extremities	37	52
Trunk	49	43
Articular	**75**	**65**
Arthralgia	11	42
Arthritis	64	23
Gastrointestinal tract	**71**	**84**
Bowel angina	70	84
Bleeding	42	42
Renal	**56**	**58**
None	25	24
Mild (microhematuria, proteinuria <300 mg/24 h)	25	15
Severe (proteinuria >2 gr/d, hematuria, oliguria, hypertension, raised plasmatic creatinine levels)	4	11
Renal insufficiency	2	8
Others		
Orchitis	4–13	–
Lung (pulmonary hemorrhage, interstitial infiltrates)	5	–
Central nervous system (headache, behavior changes, focal neurological deficit)	2–5	–

Modified from the references [4, 9]

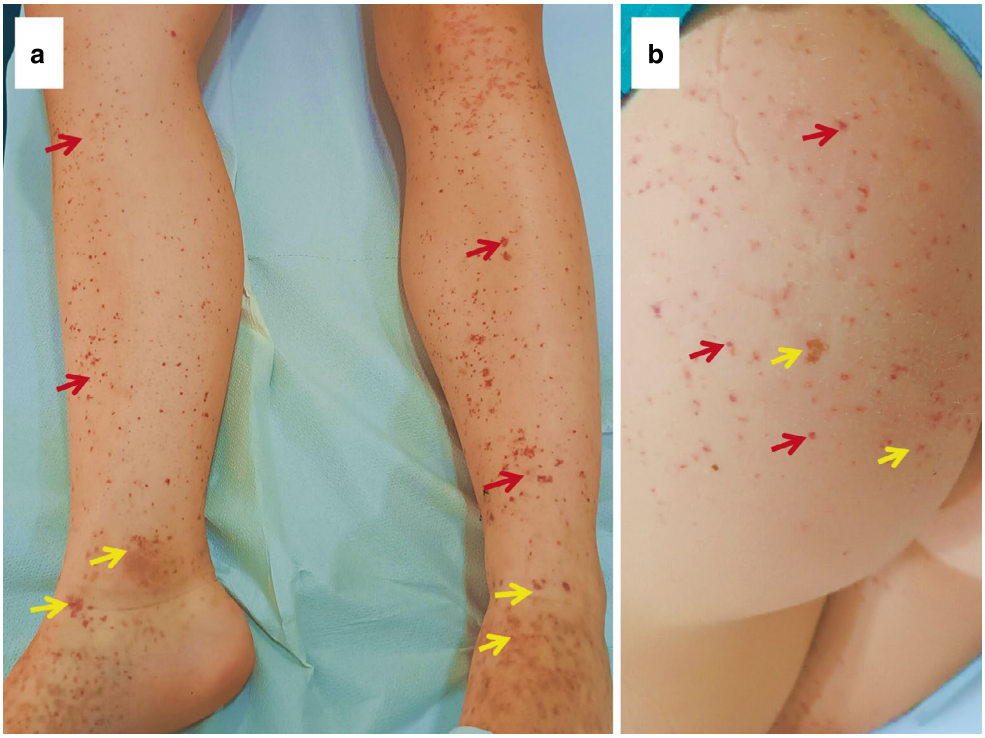

Fig. 26.1 Purpuric rash with reddish acute (red arrows) and hyperpigmented lesions (yellow arrows) in the lower limbs (**a**) and the buttocks (**b**) of a patient with IgAV

and constitutes the most serious complication of IgAV [4, 7, 9]. Glomerulonephritis, as part of IgAV, may be indistinguishable from IgA nephropathy [1]. Microscopic hematuria, the most common identifiable feature, occasionally presented as macrohematuria, is accompanied by proteinuria in about 60% of cases. Presentation as isolated proteinuria is uncommon. Glomerulonephritis associated with IgAV tends to be developed weeks or months after the onset of cutaneous purpura. Impaired kidney function is infrequent, but occurs more often in adults and is an indicator of poor long-term prognosis in this vasculitis [4, 5, 9].

Less common manifestations of IgAV include testicular pain and swelling or scrotal hematoma caused by orchitis or testicular torsion (mainly in children), and pulmonary and central nervous system involvement with alveolar hemorrhage and cerebral bleeding [4, 5, 9]. Vasculitis affecting the myocardium, ocular involvement with bilateral subperiosteal orbital hematomas, adrenal bleeding, and acute pancreatitis have been also described in IgAV.

IgAV and polyarteritis nodosa seem to occur more frequently in patients with familial Mediterranean fever (FMF). In this sense, up to 7% of patients with FMF have been reported to have IgAV, and 24–49% of children with IgAV from Turkey, Middle East, and Asian countries have been found to be carriers of mutations in the FMF causal gene (*MEFV*) [3].

IgAV in children typically has a benign and self-limiting course. However, in adult patients, IgAV tends to be more persistent and relapsing, and more frequently involves kidney. Therefore, adults often require higher doses of glucocorticoids and additional immunosuppressive drugs than pediatric patients [5].

IgAV prognosis is highly variable and depends on the extent of the renal involvement and the occurrence of severe gastrointestinal, pulmonary, and neurological complications during the early phases of the disease [4, 9]. Other identified poor prognostic factors include advanced age, previous history of infections, extent of purpuric lesions above the pelvic girdle, and presence of fever, elevation of acute phase reactant levels, anemia, and hematuria at disease onset. Some of these parameters, such as age, hematuria, and extent of the leukocytoclastic lesions, have also been associated with an increased risk of relapses [3].

Laboratory Findings

No regular laboratory parameters have been found to contribute to a definitive diagnosis of IgAV to date. Acute phase reactant parameters, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), do not seem to be useful in IgAV diagnosis. Circulating IgA levels are found elevated in half of patients during the active phase of the disease, and in a lower proportion in adults compared to children [3, 4, 9]. Complement fractions C3 or C4 may be decreased in some cases [4]. Other immunological parameters, such as serum levels of cryoglobulins, antineutrophil cytoplasmic antibody (ANCA), rheumatoid factor (RF), and antinuclear antibodies (ANA), are useful only to rule out other diseases that may present with leukocytoclastic vasculitis [3].

Because severe or refractory cases of IgAV tend to affect the kidneys and gastrointestinal tract, in order to avoid repeated biopsies, noninvasive biomarkers with high sensitivity and specificity to facilitate early detection, continuous monitoring of disease response, and prognosis have been identified [7]. In this sense, plasma coagulation factor XIII activity and neutrophil/lymphocyte ratio (NLR) have been used as biomarkers of severe gastrointestinal involvement in IgAV. Factor XIII, responsible for clot formation and wound healing, has showed a decreased activity during the acute phase of IgAV, probably due to its degradation by inflammatory enzymes. Interestingly, coagulation factor XIII administration has demonstrated to improve gastrointestinal symptoms in isolated case reports [7]. Several preclinical serum and urine biomarkers of kidney damage in IgA correlating with disease severity and disease activity have been also identified, and include kidney injury molecule-1 (KIM-1), monocyte chemoattractant protein-1 (MCP-1), β-N-acetylglucosaminidase (NAG), and urinary angiotensinogen (UAGT). Glomerular Gd-IgA1-specific antibodies, apolipoprotein M, matrix metalloproteinase-9 (MMP-9), red blood cell distribution width, pentraxin 3, alpha-smooth muscle actin (α-SMA), and c-Met (a receptor tyrosine kinase) have been additionally recognized as serum biomarkers associated with a higher risk of developing IgAV nephritis [7].

Diagnosis

The diagnosis of IgAV is primarily based on clinical criteria supported by histopathological findings. Although the absence of IgA immunofluorescence staining on biopsy does not exclude the diagnosis of IgAV [10], the majority of pediatric and adult series reported as IgAV or Henoch-Schönlein purpura lack histological and immunohistochemical changes showing vasculitic lesions with IgA deposition. However, to stablish a definite diagnosis of IgAV, the presence of palpable purpura should be followed by a skin biopsy demonstrating leukocytoclastic vasculitis (or glomerulonephritis, in case of renal involvement), with IgA deposits in direct immunofluorescence, in the presence or absence of the other typical accompanying manifestations.

In order to increase diagnostic yield of a cutaneous biopsy in suspected cases of IgAV, the skin sample should be obtained within the first 24–48 hours of the appearance of the lesions, since although leukocytoclastic vasculitis persists, IgA deposits usually disappear after 48 hours of their onset. Deposition of IgA (mainly the IgA1 subform) in the wall of capillaries and postcapillary veins of the dermis, or in the mesangium (in renal involvement), has been shown to be specific to IgAV and is not found in other forms of leukocytoclastic vasculitis [3].

A renal biopsy should be indicated in patients presenting with progression of nephropathy and worsening of proteinuria (>500 mg/24 h) or renal function (creatinine >1.5 mg/dL). Confirmation of kidney lesions is useful to indicate a more aggressive treatment. In patients with involvement of other territories, such as the gastrointestinal tract, lung, central nervous system or testicles, complementary tests should be addressed to evaluate the lesions in these territories. However, biopsies at these locations are generally not necessary if a previous histologic diagnosis has been achieved in the skin or kidney.

Differential Diagnosis

IgAV differential diagnosis should be principally made with hypersensitivity vasculitis and isolated cutaneous leukocytoclastic vasculitis, since these cutaneous forms of vasculitis affect the skin and have leukocytoclastic vasculitis as a common histological substrate. IgAV should also be differentiated from other secondary or infection-associated leukocytoclastic vasculitis, neoplasms (especially hematological), and other systemic vasculitides, especially those affecting small vessels, such as ANCA-associated vasculitis (granulomatosis with polyangiitis [GPA], microscopic polyangiitis [MPA], and eosinophilic granulomatosis with polyangiitis [EGPA]), cryoglobulinemic vasculitis, hypocomplementemic urticarial vasculitis (HUV, or anti-C1q vasculitis), as well as leukocytoclastic vasculitis associated with systemic autoimmune diseases, such as systemic lupus erythematosus and Sjögren's syndrome, among others.

All those conditions presenting with purpuric lesions of hematological origin (thrombocytopenias, blood dyscrasias, coagulation disorders, etc.) or congenital hemorrhagic angi-

Table 26.2 Clinical and histopathological differences and similarities between IgA vasculitis (IgAV)-associated glomerulonephritis and IgA nephropathy

	IgAV-associated glomerulonephritis	IgA nephropathy
General characteristics		
Extrarenal manifestations	Common	Rare
IgA nephropathy	+	+
Relatives affected	+	+
Similar geographical predominance	+	+
Raised circulating IgA levels	+	+
Age at onset >12 years	10%	26%
Palpable purpura	90%	0
Join involvement	47%	0
Abdominal pain	60%	3%
Complete remission achievement	73%	19%
Histological features		
Global sclerosis	3%	35%
Mesangial sclerosis	6%	42%
Endothelial proliferation	65%	30%
Formation of crescents	28%	19%
Thin basement membrane nephropathy	6%	0%
Type of deposits		
IgA/C3	6%	26%
IgA + IgM/C3	22%	55%
IgA + IgG + IgM/C3	53%	19%
Others		
Predominant IgG deposits	13%	0%
Linear IgG deposits	6%	0%
Capillary wall staining for IgA	70%	43%
Electronically dense deposits	Sparse, loose, widely spread in glomerular mesangium, subendothelial area, intrabasement membranes	Dense, lumpy limited in mesangium, paramesangium

Modified from the reference [11]

opathies (Rendu-Osler disease, Fabry disease, Ehlers-Danlos disease, Marfan syndrome, pseudoxanthoma elasticum, osteogenesis imperfecta, etc.), and other acquired forms must also be ruled out.

Finally, IgA nephropathy, as an isolated renal disease, has always to be considered part of the differential diagnosis of IgAV. In this sense, clinical and histopathological differences and similarities between IgAV-associated glomerulonephritis and IgA nephropathy are illustrated in Table 26.2 [11].

Table 26.3 The 1990 American College of Rheumatology criteria for the classification of IgA vasculitis (formerly Henoch-Schönlein Purpura)

Criterion	Definition
Palpable purpura	Slightly raised palpable hemorrhagic skin lesions, not related to thrombocytopenia
Age ≤ 20 years at disease onset	Patient 20 years or younger at onset of first symptoms
Bowel angina	Diffuse abdominal pain worse after meals, or bowel ischemia, usually including bloody diarrhea
Wall granulocytes on biopsy	Histologic changes showing granulocytes in the walls of arterioles or venules

To be classified as Henoch-Schonlein purpura, at least 2 of the 4 criteria are present, with a sensitivity of 87.1% and a specificity of 87.7%
Modified from the reference [13]

Classification Criteria

IgAV had been categorized as a hypersensitivity vasculitis until 1990, when the American College of Rheumatology (ACR) distinguished both conditions by developing classification criteria for each of them [12, 13]. ACR classification criteria for Henoch-Schonlein purpura (IgAV) were based on the presence of palpable purpura, age < 20 years at onset, diffuse abdominal pain (with bowel ischemia and bloody diarrhea), and a biopsy showing granulocytes in the walls of arterioles or venules. The presence of at least two of these four criteria provided sensitivity and specificity higher than 87% for classifying patients with IgAV (Table 26.3) [13].

Subsequently, the ACR classification criteria for IgAV were not considered appropriate for pediatric patients, due to lack of specificity, and therefore, in 2010, the classification criteria of the European League against Rheumatism/Pediatric Rheumatology International Trial Organization/Pediatric Rheumatology European Society (EULAR/PRINTO/PReS) were defined for pediatric patients with IgAV. The presence of predominant purpura in the lower extremities, together with one of the following parameters: abdominal pain, arthralgia/arthritis and renal involvement, with IgA deposits on histopathological examination, provided a sensitivity of 100% and a specificity of 87% for being classified as IgAV (Table 26.4) [14].

Finally, in the Chapel-Hill Consensus Conference (CHCC) for classification and nomenclature of vasculitis, IgAV was defined as a vasculitis due to small vessel immune complex (arterioles, capillaries, or venules), in which IgA deposits should be demonstrated in skin or renal biopsies [1].

Table 26.4 Final EULAR/PRINTO/PRES IgA vasculitis (formerly Henoch-Schönlein Purpura) criteria and classification definition

Criterion	Glossary	Sensitivity (%)	Specificity (%)
Purpura (mandatory)	Purpura (commonly palpable and in crops) or petechiae, with lower limb predominance[a] (not related to thrombocytopenia)	89	86
Abdominal pain	Diffuse abdominal colicky pain with acute onset assessed by history and physical examination. May include intussusception and gastrointestinal bleeding	61	64
Histopathology	Typically leukocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit	93	89
Arthritis or arthralgia	Arthritis of acute onset defined as joint swelling or joint pain with limitation on motion. Arthralgia of acute onset defined as joint pain without joint swelling or limitation on motion	78	42
Renal involvement	Proteinuria (>0.3 g/24 h or > 30 mmol/mg) or hematuria (>5/red blood cell casts/high power field)	33	70
	Purpura or petechiae (mandatory) with lower limb predominance[a] and at least one of the following: • Abdominal pain • Histopathology • Arthritis or arthralgia • Renal involvement	100	87

[a] For purpura with atypical distribution, a demonstration of an IgA deposit in a biopsy is required

Modified from the reference [14]

Treatment

There is no solid evidence to support specific therapeutic guidelines or recommendations in the majority of patients with IgAV, particularly those with glucocorticoid-resistant or refractory disease. In most cases, and especially in children, IgAV usually has a self-limiting course, requiring only resting and symptomatic medications. When relapses occur, they tend to be less intense or aggressive than the initial presentation.

Nonsteroidal anti-inflammatory drugs (NSAID) are useful in treating joint manifestations, but they should be avoided in cases of renal and gastrointestinal involvement [5]. In patients with mild or localized purpuric lesions, conservative measures with glucocorticoids at low-to-moderate doses (e.g., prednisone at $\leq$0.5 mg/kg/day) can be used for 2–4 weeks, followed by short tapering until discontinuation. In extensive skin involvement and confluent or ulcerated lesions, and organ-or life-threatening situations (e.g., with renal, intestinal, pulmonary, or central nervous system involvement), glucocorticoids, usually with methylprednisolone pulses (1 g/day, for 3 days), or prednisone at an initial dose of 1–2 mg/kg/day, for 2–4 weeks (with subsequent tapering) are recommended [5].

The role of additional immunosuppressive drugs, such as methotrexate, azathioprine, mycophenolate mofetil, cyclosporine A, and cyclophosphamide, is unclear in IgAV. However, they are usually reserved for severe or glucocorticoid-refractory cases [5]. Immunomodulatory drugs, such as colchicine and dapsone, have been reported to be useful in some refractory cases and chronic forms of IgAV [5]. Other therapeutic options in patients with severe or refractory IgAV include intravenous immunoglobulins, plasma exchange, and rituximab [5].

Of note, rituximab is a chimeric anti-CD20 monoclonal antibody widely used with good results in patients with lymphoproliferative disorders [15], systemic lupus erythematosus [16], and other systemic vasculitides with an autoimmune background, such as ANCA-associated vasculitis [17], and immune complex small vessel vasculitis, such as cryoglobulinemic vasculitis (either essential or secondary to hepatitis C virus) [18]. Rituximab has been used mainly in adult patients with IgAV and other comorbid conditions [19]. However, rituximab has also demonstrated good responses in a review series of 35 pediatric and adult patients with IgAV resistant or refractory disease to glucocorticoids or conventional immunosuppressive agents, most of them with renal involvement. In addition, retreatment in relapsing cases was followed with good disease control in all of them. Therefore, rituximab seems to be a safe and useful agent in pediatric and adult patients with IgAV resistant or refractory to glucocorticoids or other immunosuppressive drugs. This positive effect may be achieved by depleting B cells, and subsequently reducing IgA production and IgA-containing immune complexes [20]. For this reason, patients presenting with disease relapses after achieving remission with rituximab might be treated with fixed regimen analogous to the remission maintenance schedule useful in ANCA-associated vasculitis (e.g., 500 mg every 6 months), for at least 2 years [17, 20]. In order to clarify the role of rituximab for induction and maintenance of remission in IgAV, controlled clinical trials are still warranted. In this sense, a prospective randomized controlled trial evaluating rituximab for remission induction in adult patients with newly diagnosed or relapsing IgAV is currently ongoing (ClinicalTrials.gov ID: NCT05329090).

Conclusions

IgAV is a primary systemic vasculitis affecting small vessels, characterized by IgA1-dominant immune deposits, and the most frequent vasculitis in childhood. Palpable purpura due to leukocytoclastic vasculitis is invariably present. Gastrointestinal and renal involvement as IgA glomerulonephritis are considered IgAV severe manifestations. Several serum and urine biomarkers are emerging as prognostic factors in assessing potential organ-threatening involvement. IgAV diagnosis relies on clinical criteria supported by histopathologic findings. Classification criteria have been delineated for pediatric and adult patients. Apart from glucocorticoids and additional immunosuppressive agents, which are usually used in patients with severe presentations, and glucocorticoid-resistant or refractory cases, rituximab has showed promising results in patients with renal involvement and refractory situations.

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Cryoglobulinemic Vasculitis

27

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Abstract

Cryoglobulinemic syndrome is a systemic inflammatory situation characterized by the presence of cryoglobulinemia with the coexistence of ischemic lesions causing tissue damage due to cryoglobulinemic vasculitis (CV) or hyperviscosity syndrome secondary to the presence of monoclonal immunoglobulins with cryoglobulin activity. Infectious diseases, mainly chronic hepatitis C virus infection, hematologic malignancies, and autoimmune diseases, are the main associated or causative factors for cryoglobulin production. Clinical vignettes highlight heterogeneous presentations, including asthenia, arthralgia, and cutaneous, neurological, and renal involvement. Diagnostic algorithms incorporating serological and histopathological assessments have been delineated. The evolving landscape of targeted therapies and immunomodulatory interventions has been also successfully explored, emphasizing the need for treating the underlying disease in all cases in which this can be identified. In this sense, the recent HCV eradication has almost eliminated the main cause of CV to date.

Keywords

Cryoglobulinemic vasculitis · Cryoglobulins · Hepatitis C virus-associated cryoglobulinemic vasculitis

Cryoglobulinemic syndrome is a clinical disorder defined by the presence of cryoglobulins in the serum (known as cryoglobulinemia), which are immunoglobulins with the ability to reversibly precipitate at temperatures lower than 37 °C and redissolve when the temperature rises above 37 °C [1]. The quantity of cryoprecipitate, so-called cryocrit, is expressed as a percentage of whole serum. Circulating cryoglobulins can be present in healthy patients or during an acute infection. This definition distinguishes cryoglobulins from cryoproteins and cold agglutinins, autoantibodies against red blood cell antigens binding to them at cold temperatures [1]. Cryoglobulinemic syndrome was described in a case series by Meltzer et al. in 1966, with a constellation of signs and symptoms, including the triad of asthenia, arthralgia, and palpable purpura (attributed to leukocytoclastic vasculitis) [1].

In the 2012 revised International Chapel Hill Consensus Conference (CHCC) on the Nomenclature of Vasculitides, cryoglobulinemic vasculitis (CV) was defined as a sys-

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temic vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with serum cryoglobulins [2]. The number of diseases associated with CV is extensive, and infectious diseases, neoplasms, and autoimmune diseases constitute the main etiological groups [3]. In patients in whom an underlying cause cannot be determined, the label "essential cryoglobulinemia" is applied [3].

Pathogenesis

The etiopathogenesis remains unknown. However, chronic immune stimulation process in which B cells are triggered by infections, neoplasms, or autoimmune diseases to produce abnormal immunoglobulins in a setting of individual genetic susceptibility seem to play a role in the development of CV [3].

In cases of HCV-associated CV, it is known that HCV can simultaneously infect B lymphocytes and hepatocytes, since both cells share CD81, a common receptor. HCV promotes a polyclonal expansion of B cells with a subsequent differentiation to autoantibody-producing memory cells, which seem to play a role in the development of lymphoproliferative disorders. In addition, chronic antigenic stimulation can lead to overexpression and clonal expansion of B-lymphocytes, and also to promote the dysregulation of immune mechanisms leading to the development of mixed cryoglobulinemia (with CV), and ultimately to the malignant transition [3].

In 1974, Brouet et al. developed the current system of classification of the three types of cryoglobulinemia based on their immunochemical composition [4]. Type I cryoglobulins (10–15% of all cases) consist of isolated monoclonal immunoglobulins, usually IgM or IgG, and usually occur in the setting of Waldenström macroglobulinemia, multiple myeloma, and less frequently, in cases with monoclonal gammopathy of undetermined significance (MGUS). Type II and III cryoglobulins consist of two different classes of immunoglobulins grouped under the common term "mixed cryoglobulinemia." Type II cryoglobulins (50–60% of cases) are formed by a monoclonal IgM with rheumatoid factor activity that forms immune complexes with polyclonal IgG and is associated with chronic infections (mainly by HCV), lymphoproliferative and systemic autoimmune diseases. Finally, in type III cryoglobulins (25–40% of cases with cryoglobulinemia), immunoglobulins are polyclonal, with the possibility to have rheumatoid factor activity and to form immune complexes (Table 27.1) [3, 4].

Table 27.1 Brouet classification for cryoglobulinemia

Type	Current prevalence (%)	Immunoglobulins
I	10–15	Isolated monoclonal Ig (M, G, A or light chains)
II	50–60	Monoclonal Ig (M, G, A) toward polyclonal IgG (*mixed cryoglobulins with rheumatoid factor activity*)
III	25–40	Polyclonal Ig (M, G, A) (*mixed cryoglobulins with rheumatoid factor activity*)

Ig Immunoglobulin

Epidemiology

The prevalence and incidence of cryoglobulinemic syndrome are uncertain, particularly due to the heterogeneity of the underlying etiology, clinical presentations, and geographical distribution of the disease. Prevalence of cryoglobulinemia varies from 19% to 50% of hepatitis C virus (HCV)-infected patients. Clinically evident CV appears to be manifested in 15–30% of patients with cryoglobulinemia, and in 5–10% of all HCV-infected patients [5].

Since the early 1990s, CV has been mostly associated with chronic HCV infection. Therefore, HCV eradication with the use of direct-acting antivirals (DAA) during the last years has led to a radical change in the current clinical picture of cryoglobulinemia and CV, which is now mainly associated with hematologic and autoimmune conditions [6, 7].

Clinical Manifestations

Apart from cutaneous lesions, the remaining clinical manifestations of CV are protean, and often overlapping among the different types of cryoglobulinemia. Symptoms often wax and wane over time, and episodes may last weeks to months, with spontaneous remissions and exacerbations. At the initial presentation and during flares, general symptoms such as fever (of unknown origin in some patients), weakness, myalgia, and arthralgia are common.

The classical description of type I cryoglobulinemia was associated with hyperviscosity-derived manifestations, such as focal thrombotic events and catastrophic cardiovascular, pulmonary, renal, or neurological complications. However, most patients with detectable type I cryoglobulins are asymptomatic and rarely present with Raynaud's phenomenon, livedo reticularis, palpable purpura, acral and digital ischemia (Fig. 27.1a, b), and ischemic ulcers (Fig. 27.1b–d), all of them usually occurring in the lower extremities. In type II (mixed) cryoglobulinemia, cutaneous involvement as palpa-

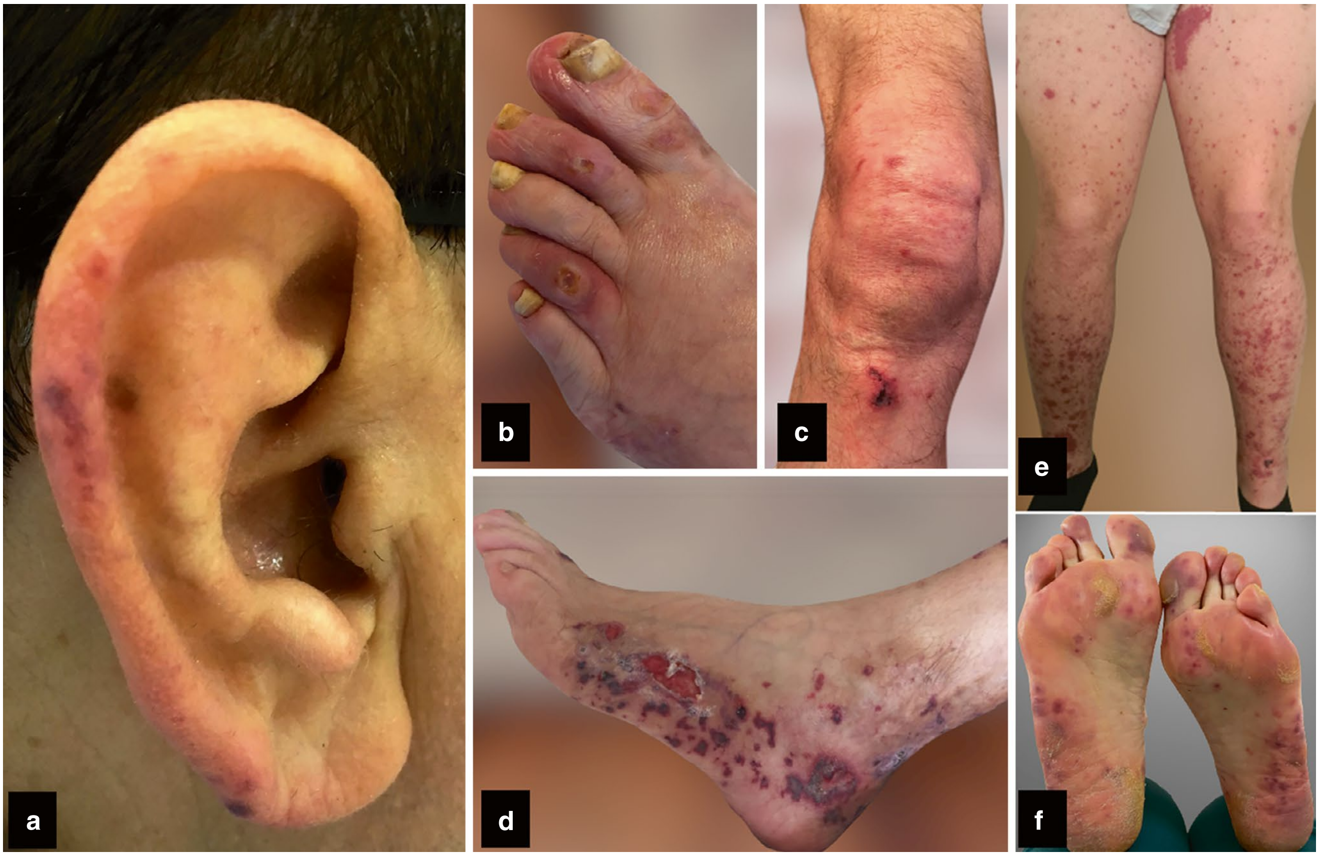


Fig. 27.1 Cutaneous lesions in cryoglobulinemic vasculitis by type I and type II cryoglobulins. (**a**–**d**) Type I cryoglobulin-associated vasculitis and ischemic lesions in a patient with multiple myeloma (at different times) involving the ear (**a**), ulcers and digital ischemia in the second and fourth toes (**b**), purpuric lesions and ulcers affecting the knee (**c**), and the external part of the left foot. (**e**, **f**) Type II (mixed) cryoglobulinemic vasculitis in a patient with a hepatitis C virus infection with purpuric lesions affecting both legs (**e**) and soles of the feet (**f**)

ble purpura is observed in more than 80% of patients (Fig. 27.1e–d).

Table 27.2 illustrates the main clinical features characteristics of type I and type II and III (mixed) CV (both HCV-associated and non-associated CV) [6, 8–11]. In CV, peripheral neuropathy, mainly as mononeuritis multiplex, is present in 22% to 62% of patients, mainly in HCV-associated CV, usually as paresthesia with painful and/or burning sensations in the lower limbs, commonly worse at night, which may precede motor involvement. The peroneal and sural nerves are pre-dominantly affected. Neurocognitive impairment is detected in about a third of patients with HCV-associated CV [10]. Clinical evidence of major end-organ damage is rare in mixed cryoglobulinemia, except for renal involvement, which is present in from 15% to 50% of patients at the time of diagnosis (more frequently in HCV-associated CV). Renal involvement ranges from abnormal urinalysis results, such as microhematuria and mild proteinuria, to nephrotic proteinuria, all features of membranoproliferative glomerulonephritis. Gastrointestinal, pulmonary, and cardiac involvement is uncommon, but typically more frequent in type II-III CV unrelated with HCV. However, acute and fatal outcomes have been reported to occur in patients presenting with mesenteric ischemia, alveolar hemorrhage, or myocardial vasculitis [3].

Laboratory Features

Although serum cryoglobulin levels do not always correlate with activity and clinical severity of cryoglobulinemic syndromes, with the exception of hyperviscosity syndrome, the diagnosis of CV is based primarily on laboratory demonstration of circulating cryoglobulins in an appropriate clinical setting suggestive of cryoglobulinemia (Table 27.2). Laboratory detection and characterization of circulating cryoglobulins will allow a proper classification and diagnosis of the type of cryoglobulinemic syndrome. False negative results in cryoglobulin detection are often caused by cold precipitation of antibodies, which can

Table 27.2 Main clinical and laboratory features of cryoglobulinemic vasculitis according to the type of cryoglobulinemia

Clinical and immunological characteristics	Type I CV [8]	Type II (mixed) HCV-associated CV [6, 10]	Type II (mixed) non-HCV CV [9, 11]	Type III (mixed) non-HCV CV [9, 11]
Age (years); median	65	59–61	63–66	60–64
Female (%)	56	68–74	69–75	74–84
Purpura (%)	69	66–82	78–85	49–56
Asthenia/fatigue (%)	–	48–71	78	61
Arthralgia (%)	28	31–52	41–72	30–90
Raynaud's phenomenon (%)	–	32	26	27
Livedo reticularis (%)	13	12	–	–
Distal ulcers/necrosis (%)	55	23	24–30	10–41
Cold-induced urticaria (%)	5	11	13	23
Sicca syndrome (%)	–	6	40	38
Peripheral neuropathy (%)	44	51–62	56–57	22–38
CNS involvement (%)	Absence/rare	28[a]	1	2–7
Renal involvement (%)	30	20–50	27–38	15–25
Gastrointestinal involvement (%)	Absence	3	6	0
Cardiac involvement (%)	Absence	5	–	–
Pulmonary involvement (%)	Absence	4	2–14	3–17
Hyperviscosity syndrome (%)	10–15	Rare	3	1
Rheumatoid factor	Normal	Positive	Positive	Positive
Complement C4	Normal/ decreased	Decreased	Decreased	Decreased

CNS central nervous system, *CV* cryoglobulinemic vasculitis, *HCV* hepatitis C virus

[a] Neurocognitive impairment

occur if the proper steps of sample processing are defective. In this sense, the first processing steps (blood collection, coagulation, and separation of serum by centrifugation) should be performed soon after blood collection and always at 37 °C. The next steps (cryocrit determination, separation and washing of the cryoprecipitate and typing of the cryoglobulin by immunofixation) should be conducted at 4 °C after at least 7 days of cold storage of the serum [3].

Histopathology

In cases of type II (mostly HCV-associated) CV, biopsies of active purpuric lesions will provide the pathological finding of leukocytoclastic vasculitis. Direct immunofluorescence microscopy of acute vasculitic lesions often reveals deposits of IgM, IgG, and/or C3 complement. When affected, kidney biopsies usually reveal membranoproliferative glomerulonephritis. In cases of peripheral neuropathy, peripheral nerve biopsy may show inflammatory occlusion of small vessels in type I cryoglobulinemia and necrotizing vasculitis of epineurial small arteries in mixed cryoglobulinemic lesions. Of note, these histological changes can be observed in arteries of any other organ affected.

Diagnosis of Cryoglobulinemic Vasculitis and Associated Diseases

The diagnosis of cryoglobulinemic syndrome should be based on the presence of the classic clinical triad of purpura, arthralgia, and weakness, as well as other organs involvement combined with serological findings. In the latter, decreased serum levels of complement C4 and/or C3 almost always occur in mixed cryoglobulinemia, and can be used as a marker of disease activity (Fig. 27.2). In patients with cryoglobulinemic syndrome and mixed type II and III cryoglobulinemia, rheumatoid factor is almost invariably present. Specific diagnostic procedures (e.g., electromyography and renal, liver or bone marrow biopsies) are indicated depending on the involved organs or territories. Table 27.3 summarizes the principal diseases associated with or causative of CV.

In type I cryoglobulinemia, hypersecretion of high levels of monoclonal cryoglobulins (IgG or IgM, and much less likely IgA and free light chains), usually due to an underlying lymphoproliferative disorder may cause hyperviscosity, which is the main clinical feature, and cryoprecipitates tend to induce microthrombotic processes within small vessels. Type I cryoglobulinemia accounts up to 10–15% patients with CV and is almost always associated with B-cell and plasma cell lymphoproliferative disorders. A large series of type I CV has reported MGUS in 44% of patients and hema-

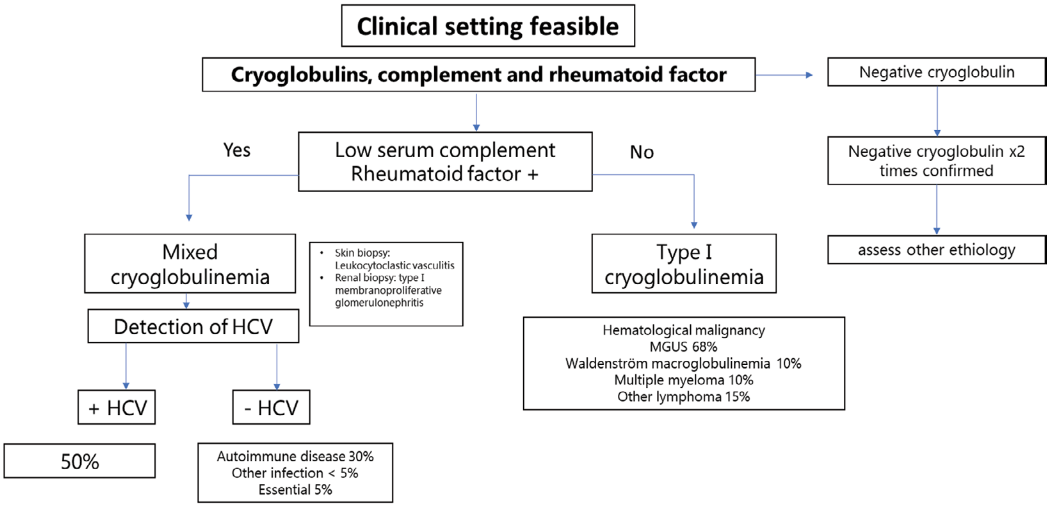

Clinical setting feasible
Cryoglobulins, complement and rheumatoid factor
Negative cryoglobulin
Negative cryoglobulin x2 times confirmed
assess other ethiology
Yes
Low serum complement Rheumatoid factor +
No
Mixed cryoglobulinemia
Skin biopsy: Leukocytoclastic vasculitis
Renal biopsy: type I membranoproliferative glomerulonephritis
Type I cryoglobulinemia
Detection of HCV
Hematological malignancy
MGUS 68%
Waldenström macroglobulinemia 10%
Multiple myeloma 10%
Other lymphoma 15%
+ HCV
- HCV
50%
Autoimmune disease 30%
Other infection < 5%
Essential 5%

Fig. 27.2 A decision mapping tree for the diagnosis of cryoglobulinemia in a clinically suggestive setting described. ***Abbreviations***: *HCV* hepatitis C virus, *MGUS* monoclonal gammopathy of undetermined significance

Table 27.3 Cryoglobulinemia and cryoglobulinemic vasculitis-associated diseases

Autoimmune disease	Malignancy	Infectious diseases
Systemic autoimmune disease • Sjögren syndrome • SLE • Mixed connective tissue disease • Systemic sclerosis • Rheumatoid arthritis • Inflammatory myopathies • Sarcoidosis • Other: PAN, ANCA-associated vasculitis, Behçet disease	**B-cell malignancies** • MGUS • Waldenström's macroglobulinemia • Multiple myeloma • Marginal zone lymphoma • Low-grade B-NH lymphoma • Lymphoplasmacytic lymphoma • Follicular lymphoma • Mantle cell lymphoma • Chronic lymphocytic leukemia • Other B-NH lymphomas	**Chronic viral infections** • Hepatitis C virus • Hepatitis B virus • Human immunodeficiency virus
Organ-specific autoimmune diseases • Ulcerative colitis • Autoimmune thyroiditis • Primary biliary cholangitis • Celiac disease • Pemphigus vulgaris • Endomyocardial fibrosis • Primary glomerulonephritis	**Other neoplasms** • Hodgkin's lymphoma • Chronic myeloid leukemia • Human herpesvirus 8 multicentric Castleman disease	**Other infectious diseases** • Epstein-Barr • Cytomegalovirus • Parvovirus B19 • Subacute endocarditis • Brucellosis • Coxiella burnetti • Leishmania • Malaria

ANCA antineutrophil cytoplasmic antibodies, *MGUS* monoclonal gammopathy of undetermined significance, *NH* non-Hodgkin, *PAN* polyarteritis nodosa, *SLE* systemic lupus erythematosus

tologic malignancies in 56% of cases, including (in order of frequency) Waldenström's macroglobulinemia, multiple myeloma, marginal zone lymphoma, chronic lymphocytic leukemia and other B-non Hodgkin lymphomas [8]. Detection of type I cryoglobulins despite the absence of typical clinical manifestations should activate the search for a lymphoproliferative disorder or monitoring a potential malignancy development.

Type II and III (mixed) cryoglobulinemia are composed by monoclonal and polyclonal immunoglobulins, respectively, and both have rheumatoid factor activity. Chronic HCV infection is the principal cause of mixed type II and III cryoglobulinemia, which accounts for 80–90% of cases of mixed cryoglobulinemia. Other viral (e.g., HBV and HIV) and bacterial infections have been described associated with mixed cryoglobulinemia (Table 27.3). In mixed CV non-associated with HCV infection, a similar proportion of cryoglobulin type (55% type II and 45% type III) has been reported [11]. In non-HCV-associated mixed cryoglobulinemia, patients with type II cryoglobulins present more frequently purpura, peripheral neuropathy, and renal involvement, as well as higher cryoglobulin levels; and lower C3 and C4 complement fractions than patients with type III cryoglobulins [9].

Whereas autoimmune diseases and hematologic diseases have been reported in 30% and 22% of patients with type II CV not related to HCV, respectively, essential type II CV has been described in 48% of subjects [9]. Autoimmune diseases associated with type II CV included (in order of frequency) Sjögren's syndrome, systemic erythematosus lupus (SLE), mixed connective tissue disease, systemic sclerosis, ulcerative colitis, rheumatoid arthritis (RA). Hematological diseases found associated with type II CV were (in order of frequency) marginal zone lymphoma, low-grade B-non-Hodgkin lymphoma, lymphoplasmacytic lymphoma, follicular lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia, and other B-non-Hodgkin lymphomas [9].

In HCV-associated CV, anti-HCV antibody and HCV RNA are found in high concentrations in the cryoprecipitate and in the necrotizing inflammatory lesions of the vessel walls [7]. Patients with chronic HCV infection and cryoglobulinemia have a higher liver fibrosis scores, higher incidence of cirrhosis, and increased risk of B lymphoproliferative disorders than those without cryoglobulinemia [3, 12]. At immunological level, patients with HCV-associated CV had significantly higher levels of rheumatoid factor and lower levels of C4 complement fraction than asymptomatic HCV-infected and circulating cryoglobulins [6].

The introduction of direct-acting antivirals achieving high HCV eradication rates has subsequently improved progression to cirrhosis and resolved the HCV-associated vasculitis. Therefore, these antiviral drugs have radically changed the approach to the management of HCV-associated CV [5–7].

Differential Diagnosis

Polyarteritis nodosa (PAN), antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides, and Sjögren syndrome are the main conditions to be considered part of the differential diagnosis of mixed CV among all systemic autoimmune diseases. Hematologic malignancies, mainly multiple myeloma, have to be considered potential causes of type I CV/cryoglobulinemic syndrome, and therefore, have to be always included in its differential diagnosis.

Differential diagnosis should include other necrotizing small-vessel vasculitides (granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis) and PAN, as a primary or idiopathic medium-sized vessel vasculitis. All the secondary forms of PAN should be considered part of the differential diagnosis of CV, including infectious (usually HBV)-associated vasculitis, autoimmune diseases (mainly SLE and RA)-associated vasculitis, and more recently, PAN-like vasculitis associated with autoinflammatory diseases (such as deficiency of adenosine deaminase 2 [DADA2] and Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic [VEXAS] syndrome) [13]. Although most cases of infectious-associated vasculitis are secondary to HBV, a limited number of cases have been reported associated with HCV infection. While PAN and its secondary forms present often with life-threatening manifestations, among which are included kidneys, liver, and splanchnic medium-sized vessels microaneurysms and stenotic/occlusive lesions, in CV is more characteristic the involvement of small-vessels. Peripheral nerve involvement is typically manifested as severe multifocal sensorimotor neuropathy in PAN, and as distal moderate sensory neuropathy in CV [14].

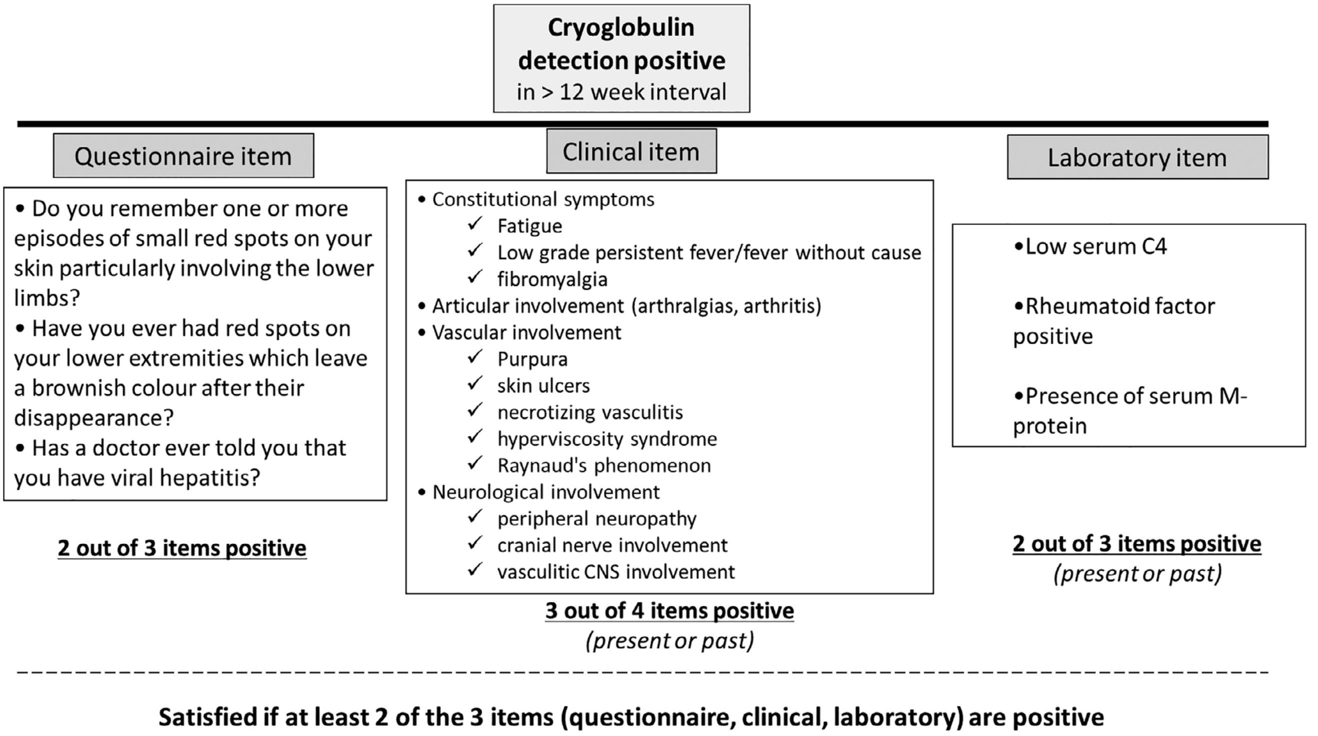
Cryoglobulinemic vasculitis and Sjögren syndrome share several clinical and serologic hallmarks, and an overlap of the two conditions may occur. On one hand, sicca or Sjögren syndrome may coexist in more than 20% patients with CV, and therefore Sjögren syndrome represents the most frequent systemic autoimmune disease in this vasculitis. On the other hand, patients with primary Sjögren syndrome may develop cryoglobulinemic features in up to 10% of cases. Symptomatic Sjögren syndrome subjects have been described to have a higher frequency of type II cryoglobulinemia, higher cryocrit and systemic inflammatory activity, increased risk of developing lymphoma, and elevated mortality [15].

Definition and Classification Criteria

Cryoglobulinemic vasculitis was defined in the 2012 CHCC as a systemic vasculitis with cryoglobulin immune deposits affecting small vessels and associated with serum cryoglobulins [2]. Skin, renal glomeruli, and peripheral nerves were considered to be frequently involved [2].

In this CHCC, the term "idiopathic" or "essential" was reserved to be used as a prefix in those cases in which the etiology of CV was unknown. Similar to other secondary vasculitides, in situations in which the etiology was known, it was allowed to include the causal agent in the name of the vasculitis (e.g., HCV-associated CV) [2].

Regarding classification criteria for cryoglobulin-associated diseases, a distinction should be made between the hyperviscosity syndrome and CV. For the type I cryoglobulins-induced hyperviscosity syndrome, no classification criteria have been defined yet. However, for CV only preliminary classification criteria are available [16]. These criteria are based on the presence of cryoglobulins in at least two determinations with an interval of more than 12 weeks. In addition, support criteria should come from a question-



Cryoglobulin detection positive
in > 12 week interval

Questionnaire item

- Do you remember one or more episodes of small red spots on your skin particularly involving the lower limbs?
- Have you ever had red spots on your lower extremities which leave a brownish colour after their disappearance?
- Has a doctor ever told you that you have viral hepatitis?

2 out of 3 items positive

Clinical item

- Constitutional symptoms
  - ✓ Fatigue
  - ✓ Low grade persistent fever/fever without cause
  - ✓ fibromyalgia
- Articular involvement (arthralgias, arthritis)
- Vascular involvement
  - ✓ Purpura
  - ✓ skin ulcers
  - ✓ necrotizing vasculitis
  - ✓ hyperviscosity syndrome
  - ✓ Raynaud's phenomenon
- Neurological involvement
  - ✓ peripheral neuropathy
  - ✓ cranial nerve involvement
  - ✓ vasculitic CNS involvement

3 out of 4 items positive
(present or past)

Laboratory item

- Low serum C4
- Rheumatoid factor positive
- Presence of serum M-protein

2 out of 3 items positive
(present or past)

Satisfied if at least 2 of the 3 items (questionnaire, clinical, laboratory) are positive

Fig. 27.3 Preliminary classification criteria for cryoglobulinemic vasculitis (adapted from De Vita et al. 2012) [16]*. *The classification criteria are based on the repeated presence of cryoglobulins and a combination of items in the categories questionnaire, clinical, and laboratory. ***Abbreviations***: *CNS* central nervous system

naire item, a clinical item, and/or a laboratory item (Fig. 27.3). These preliminary criteria were subsequently validated with good sensitivity and specificity results in a larger international patient cohort study [17].

Treatment

In HCV-associated CV, HCV clearance should be considered the main therapeutic goal. Current therapy is based on various combinations of interferon-free DAA (such as sofosbuvir, ledipasvir, daclatasvir, and simeprevir, among others), which have demonstrated very high antiviral efficacy and minimal side effects with a short treatment duration (usually 8–24 weeks). Long-term viral response associated with good control of vasculitis manifestations is sustained in most treated patients [6, 7, 18], with complete responses in 71% of them, which allows baseline immunosuppressive therapy reductions or withdrawal in most subjects. However, complete clinical and immunological responses (rheumatoid factor and cryoglobulins disappearance and complement normalization) are achieved only in about half of patients [6]. After long-term follow-up, a few proportion (up to 11%) of patients with HCV-associated CV (most of them with liver cirrhosis) may develop mild-to-severe relapses of vasculitis [7].

In active HCV-associated CV, together with DAA, glucocorticoids at high-to-moderate doses should be administrated for 2–4 weeks followed by a quick tapering until withdrawal. In severe cases, such as active cryoglobulinemic nephropathy, extensive ulcers, intestinal ischemia, severe mononeuritis or myocarditis, the additional use of plasma exchange may be effective. In refractory cases with no cryoglobulins clearance, since the polyclonal or clonal expansion of B-lymphocytes is responsible for the continuous production of immunoglobulins/cryoglobulins, the addition of rituximab (e.g., at doses and schemes of ANCA-associated vasculitis) has been reported useful [19]. In addition, the direct B-cell depleting effect seems to contribute to eliminate the HCV reservoir. Anyway, rituximab is the most widely used biologic agent for the treatment of CV regardless of the underlying etiology [19].

In patients with cryoglobulinemia associated with hematologic malignancies, asymptomatic individuals do not usually require treatment and can be managed with a watchful and waiting approach. When the hematologic disease requires treatment, or cryoglobulinemia is manifested with severe organ damage, the underlying clonal disorder should be treated with appropriate chemotherapy regimens [20]. Plasma exchange is recommended in cases of hyperviscosity syndrome due to type 1 cryoglobulinemia [20].

Conclusions

Hyperviscosity syndrome and CV are two possible manifestations of cryoglobulinemic syndrome, usually associated with different types of cryoglobulins, and in turn caused by different hematologic and systemic diseases. While type I (monoclonal) cryoglobulinemia is frequently associated with hematologic disorders, type II (mixed) cryoglobulinemia, mainly associated with chronic HCV infection, is the more commonly observed associated with CV. Treating the underlying cause of cryoglobulinemia is crucial to control the derived systemic and vasculitic manifestations. In this regard, the recent HCV eradication has almost eliminated the main cause of CV to date.

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Hypocomplementemic Urticarial Vasculitis (Anti-C1q Vasculitis)

28

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Abstract

Urticarial vasculitis (UV) is a clinicopathological condition characterized by recurrent episodes of urticaria lasting for more than 6 months, with fixed pruritic and painful lesions persisting longer than 24 h, and histopathology demonstrating leukocytoclastic vasculitis. Hypocomplementemic UV (HUV) and normocomplementemic UV (NUV) are the two differentiated forms of UV. While NUV is considered a cutaneous single-organ vasculitis, HUV or anti-C1q vasculitis has been recognized as an immune complex vasculitis affecting small vessels presenting with urticarial lesions, hypocomplementemia, and systemic extent. Extracutaneous manifestations include articular complaints, uveitis, and recurrent abdominal pain. However, renal and pulmonary involvement as glomerulonephritis and chronic obstructive pulmonary disease (COPD) are also common and associated with bad prognosis. The presence of circulating anti-C1q antibodies, and complement and immunoglobulins (Ig) deposits in or around the walls of small vessels at direct immunofluorescence constitute distinctive laboratory and immunological findings in HUV. Although HUV can be idiopathic, it can also occur associated with autoimmune diseases, infections, reactions to medications, or as a paraneoplastic syndrome. A differential diagnosis with these and other conditions presenting with urticarial lesions is mandatory. Treatment should be tailored according to the predominant clinical presentation. Smoking cessation is crucial. For cutaneous lesions, antihistamines, colchicine, dapsone, hydroxychloroquine, or low doses of glucocorticoids can be useful. In systemic forms with renal and/or pulmonary involvement, glucocorticoids have been used, usually accompanied by cyclophosphamide and other conventional immunosuppressive drugs. Recently, biologic drugs, such as anti-CD20, anti-interleukin 1, and anti-IgE agents, have been found effective in refractory cases.

Keywords

Hypocomplementemic urticarial vasculitis · Urticarial vasculitis · Anti-C1q vasculitis · Anti-C1q autoantibodies Chronic urticaria · Small-vessel vasculitis

Urticarial vasculitis (UV) is a clinicopathological condition characterized by recurrent episodes of urticaria lasting for more than 6 months, with fixed lesions persisting longer than 24 h, and leukocytoclastic vasculitis is the histopathological hallmark [1]. UV represents a continuous spectrum of disease, ranging from urticaria with minimal vasculitis to life-threatening systemic vasculitis with minimal urticaria [2]. Depending on complement levels accompanying UV, two different forms have been recognized as hypocomplementemic UV (HUV) and normocomplementemic UV (NUV). While HUV is associated with systemic involvement and

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more severe disease, NUV usually presents with a milder disease restricted to the skin [2].

The 2012 Chapel Hill Consensus Conference (CHCC) for the nomenclature and classification of vasculitides defined HUV, also named anti-C1q vasculitis, as an immune complex small vessel vasculitis characterized by the presence of vasculitis, urticaria, and hypocomplementemia affecting capillaries, venules, or arterioles, and associated with anti-C1q antibodies [3]. HUV main clinical manifestations include glomerulonephritis, arthritis, chronic obstructive pulmonary disease (COPD), and ocular inflammation [3].

Although HUV may be idiopathic, HUV cannot be considered a primary systemic vasculitis per se [3], since apart from systemic lupus erythematosus (SLE), HUV can also occur associated with other immune complex small vessel vasculitides and other autoimmune diseases, but also with infections, reactions to medications, or as paraneoplastic syndrome [4, 5].

Epidemiology

HUV is considered a rare disease, more common in women than in men (3–4 to 1), with an estimated annual incidence of 0.5 cases per 100.000 inhabitants in USA or 0.7 cases per million inhabitants (1.3 in women and 0.2 in men) in Sweden. Its prevalence in Sweden has been found of 9.5 patients per million inhabitants [4, 6]. HUV peak of incidence is observed in the fourth decade of life, and it is extremely rare in children (less than 10% of cases). NUV is more common than HUV [6]. In addition, HUV represents around 5% of cases of chronic urticaria, ranging from 3% to 20% depending on the histological definitions [2].

Pathophysiology

UV results from the formation of circulating immune complexes that deposit in or around the wall of blood vessels. Regarding HUV, 2012 CHCC classified this systemic vasculitis as mediated by immune complexes affecting small vessels [3, 7]. This pathogenic mechanism has been supported by the association of UV with certain infections, in which antigen-antibody complexes are well-defined (e.g., hepatitis B or C virus), and also by the fact that the immune complexes removal through plasma exchange is temporary associated with the resolution of urticarial lesions [7, 8]. However, most of the antigens triggering antibody formation are often unknown [5].

A region similar to collagen in C1q has been involved as antigenic target in HUV, and C1q precipitin has been identified as autoantibody. However, a definitive causal role in UV of this specific autoantibody has not been established yet. Regardless of the origin of antigen-antibody complexes, they activate the classical complement pathway, generating C3a and C5a, which leads to mast cell degranulation, and increased vascular permeability and neutrophil chemotaxis, finally leading to urticarial lesions [2, 9].

Genetic factors have also been implicated. A study on two families with HUV found mutations in the *DNASE1L3* gene, which is associated with an autosomal recessive familial form of HUV and SLE-associated HUV [4]. The role of certain proinflammatory cytokines, such as interleukin (IL)-1 or IL-6, in disease activity is still unknown. However, HUV control has been already reported with the pharmacological blockade of these cytokines, mainly IL-1 [10, 11].

Clinical Presentation

Cutaneous involvement in UV is characterized by persistent (>24 h) urticarial lesions affecting any part of the body. Lesions are usually painful, tender, burning, but above all pruritic. Urticarial changes usually exhibit a pronounced central clearing, and are often accompanied by residual hyperpigmentation after resolution (Fig. 28.1a and b). In almost a third of cases, lesions can occur as palpable purpura [8, 12]. Half of patients with UV may experience angioedema-like lesions, which is developed when vasculitis affects capillaries and postcapillary venules in the deeper layers of the dermis or submucosal tissue. Edema can be also developed in areas of sustained pressure. In these cases, the differential diagnosis with pressure urticaria and laryngeal edema has to be considered [2]. Livedo reticularis may be evident in 10–15% of cases. Less frequent presentations include erythema multiforme-like, bullous lesions and Raynaud's phenomenon [12]. Cutaneous involvement may occur before or concomitantly with systemic manifestations.

Systemic involvement is common and often associated with a decreased hemolytic activity of serum complement due to activation of the classical complement pathway [2, 7]. Musculoskeletal manifestations, such as myalgia, arthralgia, and arthritis, are the most common extracutaneous symptoms affecting 50–75% of patients. They are usually transient and migratory accompanying cutaneous lesions. Hands,

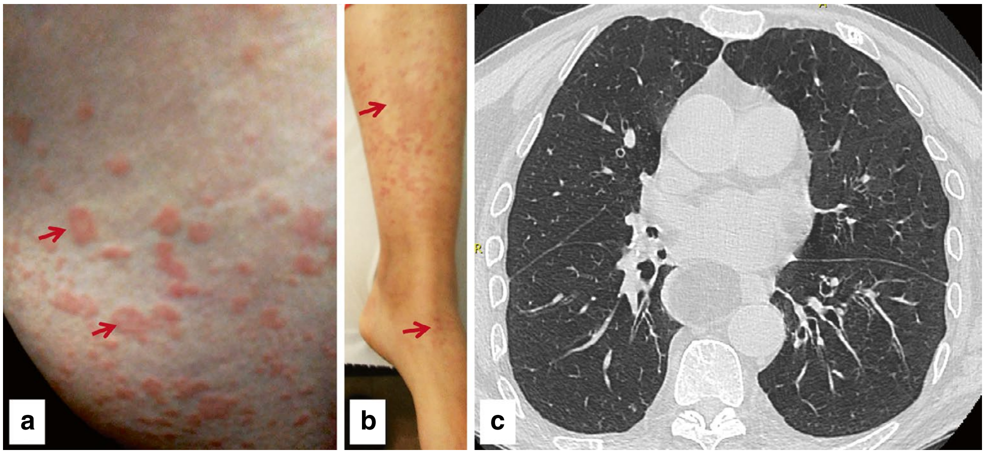

Fig. 28.1 Cutaneous and pulmonary lesions associated with hypocomplementemic urticarial vasculitis. (**a**) Acute urticarial lesions, some of them exhibiting a depressed clearing center (arrows). (**b**) Residual hyperpigmented cutaneous lesions. (**c**) Chest computed tomography showing pulmonary cysts and emphysema-related changes in peripheral areas

elbows, knees, ankles, and feet are the joints more frequently affected. While erosions are not evident, deformities such as Jaccoud's arthropathy may occur. In this regard, several cases have been reported with a syndromic picture characterized by HUV, Jaccoud's arthropathy, and cardiac (mitral and aortic) valvulopathy [2].

Renal and pulmonary involvement may be present from disease onset. However, they typically emerge as late complications of UV. Urinalysis abnormalities, either as proteinuria or hematuria, are observed in 20–30% of patients with HUV and can evolve to different stages of renal failure, including dialysis-dependent end-stage renal disease [2, 8]. HUV renal biopsies may exhibit a wide variety of histological findings, including proliferative and focal glomerulonephritis, mesangial, crescentic, or membranoproliferative patterns, as well as necrotizing vasculitis or tubulointerstitial nephritis [2, 12].

COPD and asthma are the most frequent pulmonary manifestations in UV, since they occur in about 20% of patients with HUV and 5% of those with NUV (Fig. 28.1c). While many patients with UV and COPD have a smoking history, most of them are usually diagnosed between 30 and 40 years of age, with lower pack-year history than the amount expected for COPD patients [2, 9]. Pulmonary biopsies may depict acinar destruction with foci of capillaritis and leukocytoclastic vasculitis. Reversible tracheal stenosis has been also described. A 1982 series of 16 patients with HUV already observed that 80% of patients were smokers and presented with COPD [9]. In three patients, severe COPD developed at an early age, with a relatively low pack-year history [9]. COPD in HUV has been described also in nonsmokers [2, 8, 9]. Therefore, pulmonary disease in HUV seems the result of the interaction of two significant risk factors: an immune-mediated process and smoking. On one hand, lung destruction occurs by a vasculitis phenomenon and the excessive production of neutrophil elastase, which in turn favor the development of emphysema. On the other hand, tobacco would accelerate pulmonary damage by promoting the recruitment of neutrophils. There is also evidence implicating anti-C1q antibodies, which may be directed against surfactant proteins in the lungs, since these proteins also contain a collagen-like binding region similar to C1q. This destructive cross-reactivity could be a contributing factor to the development of pulmonary disease [8, 12, 13]. Other cardiothoracic abnormalities have been infrequently reported in HUV, and include hemoptysis, pleural effusion, pericarditis, and cardiac tamponade [4].

Gastrointestinal symptoms, including abdominal pain, nausea, vomiting, and diarrhea, affect 17–30% of patients. Gastrointestinal bleeding due to vasculitis has been rarely described in patients with HUV. Ophthalmological complications in HUV range from less than 10% to 30–60% of patients. The most commonly described ocular events include episcleritis, uveitis, and conjunctivitis. Choroiditis and optic nerve atrophy have been occasionally reported [2, 8, 13]. Neurological manifestations are infrequent, but aseptic meningitis, pseudotumor cerebri, transverse myelitis, and cranial and peripheral neuropathies have been described in HUV [4].

The average duration of UV inflammatory episodes typically ranges from 1–4 weeks. Disease duration has been reported from 3 to >20 years [2, 8, 12, 13]. The course of NUV is generally benign since no permanent sequelae are generally developed. Although patients with HUV tend to have a more severe disease and experience significant morbidity, mortality is uncommon [12, 13]. The main clinical features of HUV and NUV are illustrated in Table 28.1.

Table 28.1 Clinical, laboratory, and histopathological characteristics of urticarial vasculitis according to complement levels

Characteristics	*Description*	Hypocomplementemic urticarial vasculitis (%)	Normocomplementemic urticarial vasculitis (%)
Mucocutaneous	***Urticaria-like lesions > 24 h***	96	82
	Angioedema	43	28
Extracutaneous	***Fever***	22	17
	Arthralgia	77	29
	Arthritis	43	1
	Eye	41	2
	Kidney	24	5
	Gastrointestinal tract	19	10
	Lung	28	6
	Neurological	7	1
	Heart	3	0
	Lymphadenopathy	10	1
Histopathology—Direct immunofluorescence	***Granular deposits of Ig M, G, or A along basement membrane***	96	1
Laboratory	***Increased ESR values***	75	25
	Decreased complement (C3/C4/CH50/C1q) levels	Frequent	Absent
	Detection of IgG C1q autoantibodies	50–100%	0

Note: Clinical manifestations in different organs include: eye (conjunctivitis, episcleritis, uveitis); lung (cough, dyspnea, chronic obstructive pulmonary disease); gastrointestinal tract (abdominal pain, nausea, vomiting); kidney (microhematuria, proteinuria, glomerulonephritis); neurological (pseudotumor cerebri, seizures, peripheral neuropathy); and heart (pericarditis)
ESR Erythrocyte sedimentation rate, *Ig* Immunoglobulin
Adapted from reference [4]

Laboratory Findings

The most common laboratory abnormalities in UV include an elevated erythrocyte sedimentation rate (ESR) and hypocomplementemia (Table 28.1). Although elevated ESR is observed in approximately 75% of patients, it is not specific and does not correlate with the disease severity. In contrast, hypocomplementemia is a sensitive marker of systemic inflammation and correlates with disease severity [8, 13]. In patients with HUV, decreased levels of C1, C1q, C2, C3, and/or C4, as well as a reduction in CH50/100, are usually observed due to the activation of the classical complement pathway. C1q is often lower than C1r or C1s. C1q, C3, and C4, which probably are the most frequently reduced components, and their levels remain stable at different time points along the process. Decreased levels of C1q are accompanied by normal levels of C1 inhibitor. Circulating antibodies against the collagen-like region of C1q (C1q precipitins) are present in most patients with HUV. Although this test is not routinely available, anti-C1q autoantibodies can be detected by enzyme-linked immunosorbent assay (ELISA). Specificity and positive predictive value of the reduced levels of C1q are not clear, since patients with SLE may also have decreased levels of C1q without suffering UV [4, 14].

Additional laboratory findings in UV include polyclonal hypergammaglobulinemia, detection of circulating immune complexes, cryoglobulins, rheumatoid factor, or antinuclear antibodies (ANA), and false-positive syphilis serologies. Additionally, anemia of chronic disease (less commonly hemolytic anemia), and leukocytosis with neutrophilia can also be observed [4].

Histopathology

Because UV can be difficult to distinguish from allergic urticaria, a confirmatory diagnosis of UV requires a skin biopsy. Cutaneous sample should be obtained from active or new lesions, preferably within the first 48 hours, since the likelihood of detecting characteristic histopathological features of UV is higher in recent biopsies. Skin biopsy typically reveals a neutrophilic perivascular predominance and leukocytoclasia in small vessels of the papillary and reticular dermis, especially in postcapillary venules. Subepidermal edema (causing urticaria) is often observed. Cutaneous histopathological changes in UV reflect a dynamic pattern, and while in the early stages, eosinophils may be evident along with endothelial cell edema, leading to the extravasation of red blood cells due to vascular rupture, in later stages, the infiltrate becomes predominantly mixed, of mononuclear appearance [7, 8].

Direct immunofluorescence (DIF) in HUV is characterized by a constant presence of fibrin, complement, and immunoglobulins (G, A, or M) deposits in or around the walls of small vessels (capillaries, venules, arterioles). Granular deposits of C1q in the walls of capillaries are also common. Although these findings may be also observed in non-affected skin and in biopsies from SLE patients, this distinctive pattern supports an accurate diagnosis of UV, differentiating it from neutrophilic dermatoses and urticarial lesions with similar presentations [4].

Diagnosis

In patients with recurrent pruritic and painful urticarial lesions, UV diagnosis should be obtained after a thorough medical history focused in collecting concomitant symptoms of autoimmune diseases, previous infections, cancer, or drugs intake. Raised acute phase reactants and low circulating complement levels, together with a cutaneous biopsy depicting leukocytoclastic vasculitis and immunoglobulins and complement deposition in/around the blood vessels, will provide a definite diagnosis of NUV or HUV (depending on the complement levels).

Associated Conditions

Various conditions associated with UV have been described. Among immune-mediated diseases, SLE shares clinical and laboratory features with UV (e.g., arthritis, glomerulonephritis, skin lesions, and presence of ANA, hypocomplementemia, and anti-C1q antibodies). HUV presentation has been described in patients with SLE, mainly in those with longstanding disease. Conversely, UV patients may also develop symptoms mimicking SLE. Although certain manifestations, such as angioedema, COPD, or ocular involvement, are almost exclusive of UV, these observations highlight the complex interplay between these two different and (at the same time) overlapping conditions. In this sense, some authors theorize about HUV being part of the spectrum of SLE itself [4, 8, 15].

UV has also been described in patients with Sjögren's syndrome, rheumatoid arthritis, serum sickness, or complement defects, such as C3 or C4 primary deficiencies, or vasculitis associated with C3 nephritic factor (an IgG autoantibody binding to C3 convertase). Other immunological conditions in which UV has been reported include monoclonal gammopathies, cryoglobulinemia, membranous glomerulonephritis, immune thrombocytopenic purpura, Hashimoto's thyroiditis, eosinophilic pneumonitis, cryopyrinopathies, cold urticaria, Crohn's disease, Cogan's syndrome, or IgG4-related disease [4, 16].

Different infectious agents, such as hepatitis B or C viruses, *Coxiella burnetii*, *Borrelia burgdorferi*, Epstein-Barr virus, or SARS-CoV-2, have been associated with the development of UV, as well as multiple drugs (e.g., sulfamethoxazole, procainamide, valproate, atenolol, hydralazine, cimetidine, fluoxetine, paroxetine, ciprofloxacin, infliximab, glatiramer, or hyaluronic acid dermal filler agents), serum sickness, and paraneoplastic phenomena associated with hematological malignancies (e.g., monoclonal gammopathies, multiple myeloma, Hodgkin lymphoma, acute non-lymphocytic leukemia, myeloid leukemia, myeloproliferative syndromes) and solid tumors (e.g., testicular teratoma, colon adenocarcinoma) [4, 5, 17, 18].

Differential Diagnosis

The main conditions that should be included in the differential diagnosis of UV are illustrated in Table 28.2. These include acute spontaneous (classic) urticaria, chronic sponta-

Table 28.2 Differential diagnoses of urticarial vasculitis

Disease	Cutaneous and systemic manifestations	Histopathologic features	Direct immunofluorescence	Other complementary tests
Urticarial vasculitis	Painful and itching urticarial plaques often last >24 h, signs of acute lesions of leukocytoclastic vasculitis, and residual hyperpigmented lesions. Possible association with concurrent angioedema and purpuric lesions Systemic: Joint, ocular, and COPD manifestations	Histological signs of urticaria (dermal edema) and vasculitis (superficial and deep perivascular and interstitial neutrophilic infiltrate and leukocytoclasia)	Immunoglobulins and complement deposition in or around blood vessels of the upper dermis and/or at the dermal-epidermal junction	Hypocomplementemia (total complement, C3, C4, and C1q levels) in HUV forms. Possibly associated with anti-C1q antibody. Increased acute phase reactants levels
Acute spontaneous (classic) urticaria	Circumscribed, raised, erythematous plaques, often with central pallor intensely itchy. Pruritus symptoms often most severe at night. Angioedema can be present. Total duration <6 weeks	Dermal edema, blood vessel dilatation, and a mild perivascular infiltrate predominantly consisting of monocytes and CD4 lymphocytes	Negative for immune deposits	No specific abnormalities

(continued)

Table 28.2 (continued)

Disease	Cutaneous and systemic manifestations	Histopathologic features	Direct immunofluorescence	Other complementary tests
Chronic spontaneous urticaria	Transient wheals (lasting <24 h), absence of purpuric features. Resolution without hyperpigmented residual. Total duration ≥6 weeks	Dermal edema with lymphocytic and eosinophilic infiltrates without signs of vasculitis	Negative for immune deposits	Autologous serum skin test, basophil activation and histamine release assays, D-dimer, total IgE levels
Urticarial allergic contact dermatitis	Pruritic edematous plaques, papules, and vesicles lasting longer than 24 h (often persisting for days), urticated erythema with excoriations	Dermal perivascular lymphocytic/eosinophilic infiltrates with or without neutrophils, without signs of vasculitis	Negative for immune deposits	Patch testing, specific and global IgE levels
Neutrophilic urticarial dermatoses	Reddish-pale macules, papules, or slightly elevated plaques (not persistent erythematous wheals, purpura, angioedema, or facial swelling). Urticarial lesions generally resolve within 24 h Systemic: Often associated with systemic diseases, including adult-onset Still's disease, SLE, and Schnitzler syndrome	Neutrophilic epidermotropism, extending into the epithelial zone of the epidermis, hair follicles, sebaceous, and sweat glands. No edema or vasculitic changes	Negative for immune deposits	Increased acute phase reactants levels. Positive markers for associated systemic diseases
Immune complex small-vessel vasculitides (IgA vasculitis, ANCA-associated vasculitis, cryoglobulinemic vasculitis)	Palpable purpura (main lesions). Other changes include necrotic-ulcerative lesions and hemorrhagic (confluent) blisters Systemic: Arthralgia/arthritis, peripheral nerve, gastrointestinal tract and renal involvement (depending on the vasculitis)	Leukocytoclastic vasculitis involving small vessels	Perivascular IgA-dominant deposits (in IgA vasculitis). Negative or pauci-immune staining (in other vasculitides)	Circulating IgA levels increased in half of patients. Other immunological markers (ANA, ANCA, rheumatoid factor, antiphospholipid antibodies, cryoglobulins, complement) have to be normal or negative in IgA vasculitis, but positive in the other small vessel vasculitis
Cryopyrin-associated periodic syndromes (CAPS)[a]	Non-pruriginous urticarial lesions (edematous lesions, patches, papules, or plaques) on trunk, extremities and face. Exacerbated by exposure to cold (in FCAS2). Systemic: Fever, joint involvement, sensorineural hearing loss, conjunctivitis/uveitis, aseptic meningitis, secondary amyloidosis	Dermal (perieccrine and perivascular) neutrophilic infiltrates with leukocytoclasia, without signs of vasculopathy or vasculitis	Negative for immune deposits	Increased acute phase reactants levels. Mutations in the *NLRP3* gene
Schnitzler syndrome	Chronic non-pruriginous recurrent urticarial rash on trunk and upper extremities, persisting 4–36 h. Systemic: Fever, arthralgia, hepatosplenomegaly, lymphadenopathy	Neutrophilic urticaria (most common). Other features include spongiotic dermatitis and leukocytoclastic vasculitis (in 25% patients)	Negative for immune deposits	Monoclonal gammopathy, increased acute phase reactant levels
Bullous pemphigoid	Blisters and erosions on erythematous skin Systemic: Oral ulcers, conjunctivitis	Subepidermal blisters, eosinophilic dermal infiltrates	Linear homogeneous IgG/C3 deposits along the basement membrane. In the early stages, only C3 may be present	Circulating anti-BP180 and anti-BP230 antibodies

(continued)

Table 28.2 (continued)

Disease	Cutaneous and systemic manifestations	Histopathologic features	Direct immunofluorescence	Other complementary tests
Lupus erythematous tumidus	Urticarial erythematous-edematous lesions on photoexposed areas. Healing process without hyperpigmented/ecchymotic sequelae	Perifollicular and interstitial mucin deposits, perivascular and/or periadnexal lymphocytic infiltrates, without vasculitic changes	Linear/granular IgG/IgM along the dermal-epidermal junction	ANA positivity
Wells syndrome (eosinophilic cellulitis)	Urticarial erythematous-edematous lesions (occasionally with annular configuration)	Dermal superficial and deep perivascular (occasionally extended to subcutaneous tissue or underlying muscle) interstitial infiltrates with lymphocytes, histiocytes, giant cells and abundant eosinophils. The eosinophil degranulation forms flame figures with extensive interstitial mucin. No vasculitis	Negative for immune deposits	Acute phase reactants mildly elevated
Erythema multiforme	Symmetrical, red, raised skin patchy lesions all over the body, often looking like "targets" (dark circles with purple-grey centers). Recurrent episodes usually lasting for 2–4 weeks. Thought to be an allergic reaction to drugs, vaccines, or infections (often following herpetic reactivations) Systemic: Fever, fatigue, joint pain	Epidermal necrosis, dermal lymphohistiocytic infiltrates, without vasculitic features	Granular IgM/C3 deposits and fibrin within vessel walls	None specific
Cutaneous mastocytosis	Maculopapular cutaneous mastocytosis or urticaria pigmentosa (the form more similar to UV) is characterized by yellowish to red-brown macules or papules, predominantly affecting the trunk and extremities	Dermal infiltrates, also affecting deep dermis in a periadnexal and perivascular distribution, with spherical or spindled mast cells and scattered eosinophils	Negative for immune deposits	Positive Darier's sign (appearance of an urticarial wheal after rubbing the skin lesions), increased levels of increased serum tryptase levels, c-kit detection at immunohistochemistry

ANCA antineutrophil cytoplasmic antibody, *COPD* chronic obstructive pulmonary disease, *FCAS2* familial cold autoinflammatory syndrome 2, *Ig* immunoglobulin

[a] Mild phenotypes of cryopyrin-associated periodic syndromes (CAPS) include familial cold autoinflammatory syndrome 2 (FCAS-2) and Muckle–Wells syndrome

Adapted from references [4, 7, 12, 19]

neous urticaria, urticarial allergic contact dermatitis, neutrophilic dermatoses, autoinflammatory conditions (such as cryopyrin-associated periodic syndromes or CAPS and Schnitzler syndrome), other systemic immune complex small vessel vasculitides (such as IgA vasculitis, ANCA-associated vasculitis and cryoglobulinemic vasculitis), bullous pemphigoid, lupus erythematosus tumidus, Wells syndrome (eosinophilic cellulitis), erythema multiforme, and cutaneous mastocytosis [4, 7, 12, 19].

After the COVID-19 pandemic, urticarial syndromes associated to acute COVID-19 and anti-SARS-CoV-2 vaccine have emerged to be considered as part of the differential diagnosis of UV [4]. While in SARS-CoV-2 infections, the urticarial rash usually lasts >24 h, and cutaneous histology reveals an interface dermatitis, dermal edema, and lymphocytic/eosinophilic infiltrates, in urticarial reactions secondary to vaccinations, acute urticarial lesions tend to last <24 h, with histological features of lymphocytic/eosino-

Table 28.3 Diagnostic criteria for hypocomplementemic urticarial vasculitis [9]

Major criteria	– Recurrent urticaria for at least 6 months – Hypocomplementemia
Minor criteria	– Biopsy evidence of vasculitis showing predominantly neutrophilic infiltrate (leukocytoclastic) – Arthritis or arthralgia – Glomerulonephritis – Ocular inflammation (uveitis or episcleritis) – Recurrent abdominal pain – Pulmonary disease (e.g., infiltrates, fixed obstructive disease) – Positive anti-C1q antibodies, specifically low levels of C1q

Both major criteria and at least two minor criteria should be met for diagnosis

philic infiltrates and dermal edema. No vasculitis changes or immune deposits at DIF have been observed in any of both situations [4].

Diagnostic/Classification Criteria

UV was first described in 1973 by McDuffie et al. as a clinicopathological condition with urticaria and leukocytoclastic vasculitis at histology [1]. Subsequently, in 1982, Schwartz et al. postulated the potential role of the complement system and proposed the diagnostic criteria for HUV, for which the two major criteria (recurrent urticaria for at least 6 months and hypocomplementemia) were required, together with at least two minor criteria and exclusion of an autoimmune disease (Table 28.3) [9].

In the 1990 American College of Rheumatology classification criteria for hypersensitivity vasculitis, UV was in an undefined category since these criteria only include cases of small vessel (leukocytoclastic) vasculitis secondary to drug intake presenting with palpable purpura or maculopapular (not urticarial) rash [20]. The term “hypersensitivity vasculitis” was discontinued at the 2012 CHCC for the nomenclature and classification of vasculitides. In 2012, HUV was also named “anti-C1q vasculitis.” It was defined as a vasculitis accompanied by urticaria and hypocomplementemia, and classified among the immune complex systemic small-vessel vasculitides [3]. Since hypocomplementemia and urticaria may occur in other immune complex small vessel vasculitides and in those vasculitis associated with SLE and other systemic autoimmune diseases, in these clinical settings, the mechanistic term “anti-C1q vasculitis” is preferred to HUV [3]. The 2018 dermatologic addendum of 2012 CHCC for nomenclature of cutaneous vasculitis distinguished NUV from HUV, and NUV was defined as a single-organ vasculitis limited to the skin (without systemic extent), with normal complement levels, and absence of anti-C1q antibodies [7]. However, no specific criteria were established [7].

Treatment

Therapeutic strategies for UV are not standardized since the choice of medications depends on the systemic involvement and disease severity. All patients, but mainly those with COPD, should be advised to quit smoking and avoid its exposure. Bronchodilators may be useful in COPD. Indeed, a prompt association of UV with another systemic process (autoimmune, infectious, or neoplastic) or drug intake is crucial to be identified, since the specific therapy of the concomitant condition often resolves vasculitic manifestations.

Cutaneous and articular involvement can be initially managed with antihistamines and nonsteroidal anti-inflammatory drugs, respectively. Colchicine, dapsone, hydroxychloroquine, or low doses of glucocorticoids can be added to improve control. In severe or extensive acute cutaneous forms, high doses of glucocorticoids and even plasma exchange may be necessary. Life-threatening angioedema will often require iv. methylprednisolone and sc. adrenaline [12].

In HUV with renal and/or pulmonary involvement, glucocorticoids are recommended (usually prednisone at 1 mg/kg/day). Cyclosporine A has been effectively used in these situations. In cases presenting with COPD, cyclophosphamide and mycophenolic acid/azathioprine have been used as remission and maintenance remission regimens, respectively. In patients with kidney involvement and abnormal renal biopsy, similar schemes to those used in SLE nephropathy are advised [12].

In recent years, the benefits of anti-CD20 (rituximab), anti-IL-1 (anakinra, canakinumab), anti-IL-6 (tocilizumab), and anti-IgE (omalizumab) have been described in UV cases refractory to previous treatments [13]. A multicentric international series of 38 patients with UV (23 of them with HUV) treated with anti-CD20 ($n = 23$), anti-IL-1 ($n = 14$), and anti-IgE ($n = 10$) in association with glucocorticoids (at a median prednisone dose of 17.5 mg/day) showed complete and partial responses in 43% and 32% of cases, respectively, with significant reductions in the daily dose of glucocorticoids [11]. All biologic agents exerted similar benefits in about 85% of cases for cutaneous and extracutaneous manifestations. While most patients with HUV forms and all patients with renal involvement were treated with anti-CD20, IL-1-blockers were the drugs with a lower proportion of lack of cutaneous response [11].

Conclusions

UV is a clinicopathological condition characterized by recurrent episodes of urticaria and a histopathological evidence of leukocytoclastic vasculitis. Among the two differentiated forms of UV, NUV is considered a cutaneous single-organ vasculitis, and HUV or anti-C1q vasculitis has been recognized as an immune complex vasculitis affecting small vessels and characterized by urticarial lesions and hypocomplementemia. Systemic manifestations are typically present in HUV. Renal and pulmonary involvement as glomerulonephritis and COPD are common and associated with bad prognosis. Because HUV can occur associated with autoimmune diseases, infections, reactions to medications, or as paraneoplastic syndrome, a differential diagnosis with these and other conditions presenting with urticarial lesions is crucial. The presence of circulating anti-C1q antibodies, and complement and immunoglobulins deposits in or around the walls of small-vessel at DIF constitute distinctive laboratory and immunological findings in HUV. Treatment has to be tailored according to the predominant clinical presentation. Smoking cessation is critical in all patients. For cutaneous lesions, antihistamines, immunomodulatory drugs, or low doses of glucocorticoids can be useful. In systemic forms with renal and/or pulmonary involvement, glucocorticoids have been used, usually accompanied by cyclophosphamide and other conventional immunosuppressive drugs. Recently, biologic drugs, such as anti-CD20, anti-IL-1, and anti-IgE agents, have been used in refractory cases with promising results.

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29

Single-Organ Vasculitis

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and Gary S. Hoffman

Abstract

Single-organ vasculitis (SOV) is a category of vasculitis adopted at the 2012 International Chapel Hill Consensus Conference (CHCC) on the nomenclature of vasculitides that encompasses a group of diseases in which vasculitic involvement is confined to a specific organ, system, or territory. SOV may be localized in focal sites (e.g., aorta, mammary, genitourinary, and abdominal structures), or affect structures in a diffuse or multifocal fashion (e.g., isolated forms of central nervous system, cutaneous and retinal vasculitis). Focal SOV are usually incidentally found in evaluations for malignant or infectious conditions. Whereas the resection of the inflammatory lesion may resolve the inflammatory process in focal SOV, systemic immunosuppressive or immunomodulatory therapy is usually required in diffuse SOV. Because the territories targeted in systemic vasculitis may also be affected in SOV, SOV diagnosis always requires to exclude a systemic illness and also to reassure that it is not a limited expression of a systemic vasculitis. Except for some forms of aortic, gastrointestinal, or urologic SOV, which can be associated with local rupture or obstruction with severe or fatal consequences, the prognosis of focal SOV in other locations is usually favorable. In some focal SOV forms, certain clinical, laboratory, and histopathologic features may contribute in distinguishing isolated from systemic vasculitis, and subsequently, in developing diagnostic and therapeutic strategies.

Keywords

Vasculitis · Single Organ Vasculitis · Localized vasculitis
Focal · Diffuse · Primary central nervous system angiitis
Cutaneous vasculitis

The systemic vasculitides are heterogeneous and complex diseases that have the inflammation of blood vessels as common histopathological hallmark [1]. Vascular inflammation may be also localized in single organs, systems, or territories. These simple and confined vasculitis forms are named single organ vasculitis (SOV), also known as isolated or localized vasculitis [1–3].

SOV lesions may be focal or diffuse (Fig. 29.1). Focal forms of SOV have been found limited to single sites, such as the aorta [4–6], mammary tissue [7], gastrointestinal territories [8, 9], gynecologic [10], testicular [11] and other urogenital structures [3], and are often incidentally diagnosed in resected tissues because of suspicion of cancer, infections, or other unrelated abnormalities. SOV affecting organs or systems in a diffuse or multifocal fashion have been described involving the central nervous system (CNS) (e.g., primary CNS vasculitis), skin (e.g., different forms of isolated cutaneous vasculitis), peripheral nerves, calf muscles, and isolated vasculitis of retinal, coronary, and pulmonary vessels [2, 12]. Overall, focal forms of SOV may be resolved after resection of the vasculitic lesion. However, diffuse SOV cannot be surgically removed and usually require systemic therapy, because of a chronic and relapsing course (e.g., isolated cutaneous vasculitis) or associated morbidity and mortality (e.g., retinal vasculitis, primary CNS vasculitis) [2].

Because systemic vasculitis can affect all the territories in which SOV has been reported to occur, and occasionally, a localized disease can evolve to a systemic form, the establishment of a definite diagnosis of SOV requires the isolated

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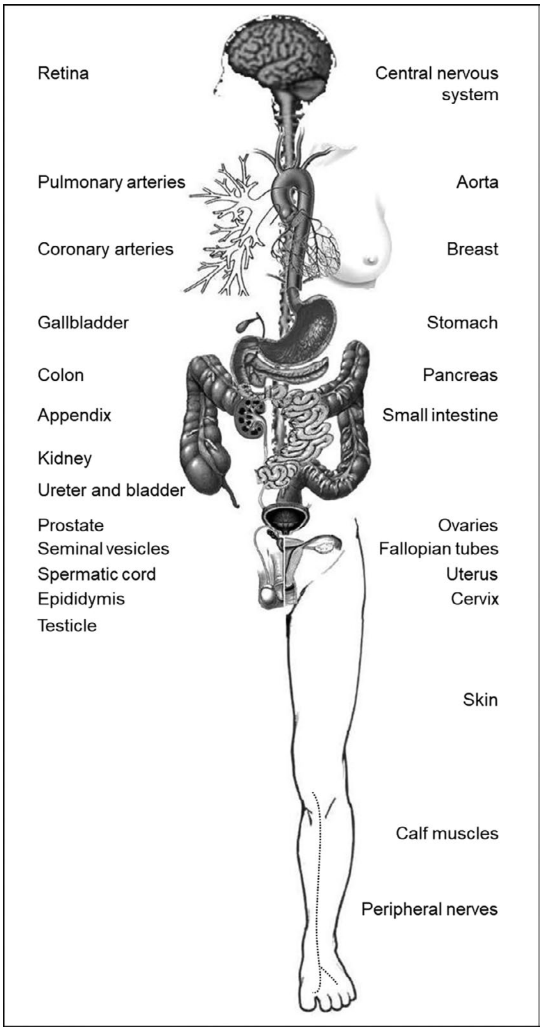

Fig. 29.1 Organs and structures affected by single-organ vasculitis. *Modified with permission from reference [2]

nature of the disease to be confirmed after long-term surveillance, which has been proposed to be a minimum of 6 months [2].

This chapter covers both types of SOV, with particular emphasis on focal forms of SOV and their distinction from systemic vasculitides involving the same territories. In addition, a brief review of diffuse SOV forms affecting CNS, cutaneous, and retinal vessels is described.

Definition and Categorization of Single Organ Vasculitis

The 2012 International Chapel Hill Consensus Conference (CHCC) on the nomenclature of vasculitides adopted new categories and adapted the existing nomenclature by modifying names and definitions of the different types of vasculitis [1]. Apart from the previous systemic vasculitis groups divided according to the vessel size in large-, medium-, and small-vessel vasculitis, new categories included variable vessel vasculitis, vasculitis associated with systemic disease, vasculitis associated with probable etiology, and SOV [1].

SOV was defined as vasculitis affecting arteries or veins of any size in a single organ, with no features indicating that these vasculitic changes are a limited expression of a systemic vasculitis. As previously reported, vasculitis distribution was divided in focal (or unifocal) or diffuse (or multifocal) within an organ or organ system [1, 2]. Clinical, laboratory, and pathologic features were found useful in distinguishing SOV from an isolated expression of systemic vasculitis [1, 2].

2012 CHCC special considerations included to reclassify vasculitis extent in patients originally diagnosed with SOV later developing additional manifestations suggesting a systemic process [e.g., cutaneous arteritis later becoming polyarteritis nodosa (PAN)], as well as to emphasize that the discovery of vasculitis confined to a specific organ may also reflect a limited expression of a systemic vasculitis rather than a real SOV [e.g., renal limited vasculitis is considered a limited form of microscopic polyangiitis (MPA)], without implying that the limited inflammation had to subsequently evolve into systemic disease [1].

With regard to the nomenclature, the names reserved for systemic vasculitides [e.g., PAN, giant-cell arteritis (GCA) or granulomatosis with polyangiitis (GPA)] should not be used for SOV, since the names for SOV must be descriptive and include the organ and vessel type involved. Several examples of SOV names include cutaneous arteritis, cutaneous small-vessel vasculitis, CNS vasculitis, or ovarian arteritis [1, 2]. It was previously suggested also adding the histologic description, as granulomatous, non-granulomatous, or others, in the SOV name (e.g., cutaneous leukocytoclastic, angiitis (CLA), non-granulomatous vasculitis of the cervix) [2].

Focal Single Organ Vasculitis

Isolated Aortitis

The aorta and its main branches are almost invariably involved in large-vessel vasculitides, such as GCA and Takayasu's arteritis. Other systemic vasculitides and autoimmune conditions may affect also large vessels [4]. Aortic SOV is mainly found in the aortic root and arch, and has been usually discovered incidentally at histopathological examination after surgery of aortic aneurysm resection or aortic valve reconstruction (Fig. 29.2), or at autopsy [4]. Aortic SOV is diagnosed at a mean age of 60–71 years. Females are affected from 1.4 to 3.2 times more frequently than males. When aortic dissection (usually affecting the

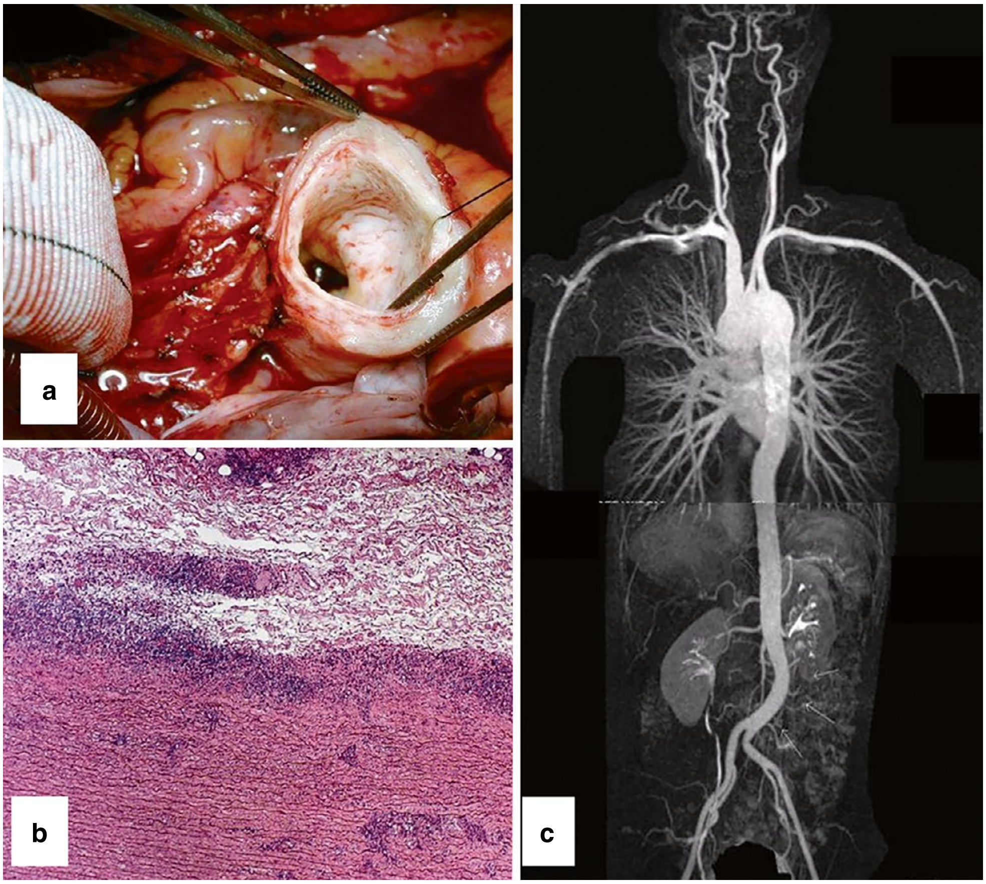

Fig. 29.2 Isolated aortitis. Vasculitis involving the aorta was unexpectedly found in a 64 year-old female patient who required surgery for aortic regurgitation and a thoracic aortic aneurysm. No past history of vasculitis or other systemic autoimmune diseases were recalled. (**a**) The aortic wall was 12 mm thick at surgery (normal ~1.5 mm). (**b**) Histology revealed intense mononuclear cell infiltration and necrosis of muscular layer with matrix disruption. (**c**) Magnetic resonance angiography after surgery did not reveal any abnormalities in the remainder of the aorta or branch vessels (except for the graft in the ascending aorta and aortic arch), and over 8 years of follow-up without receiving immunosuppressive drugs, no new lesions were noted. *Modified with permission from Hernández-Rodríguez J. and Hoffman GS. Single Organ Vasculitis. In Hoffman GS, Langford CA, Weyand CM, and Goronzy JJ (Ed). Inflammatory Diseases of Blood Vessels. John Wiley and Sons 2012

ascending aorta) is the first sign of isolated aortitis, mortality is high (68%) [2, 4–6].

The two initial retrospective surgical pathology series describing aortic SOV, at the Cleveland Clinic (Cleveland, OH) and Mayo Clinic (Rochester, MN), included 1717 thoracic aorta specimens from patients undergoing surgery for aortic abnormalities or coronary artery disease. The isolated aortitis prevalence was of 4.3% [4] and 8.8%, respectively [5]. Most patients were treated with surgery alone, and only a 5–24% of them developed aneurysms in other segments of the aorta after long-term follow-up. However, none of the 5–31% patients treated with glucocorticoids developed additional aortic abnormalities [4, 5]. From this experience, a remarkable proportion of patients in whom an isolated aortitis was discovered could be only observed without receiving systemic therapy. However, all patients should be screened angiographically searching for arterial lesions beyond the inflamed aorta. In addition, a watchful follow-up including sequential vascular imaging studies should be pursued to detect new lesions in large vessels over time [2, 6].

Vasculitis of the Breast

Mammary vasculitis has been rarely reported as part of both systemic vasculitis and SOV. In a review of 34 patients in whom vasculitis found in mammary tissue led to the diagnosis of either isolated ($n = 18$) or systemic vasculitis ($n = 16$) found that constitutional and musculoskeletal symptoms occurred almost exclusively in patients with systemic disease. Patients with systemic vasculitis had higher erythrocyte sedimentation rates (ESR) and lower hemoglobin levels than those with SOV. Age, breast manifestations (duration of symptoms prior to diagnosis, pain or painless masses, unilateral or bilateral involvement), and histological features (Fig. 29.3a) could not help in differentiating systemic from SOV involving the breast. Glucocorticoid therapy was only

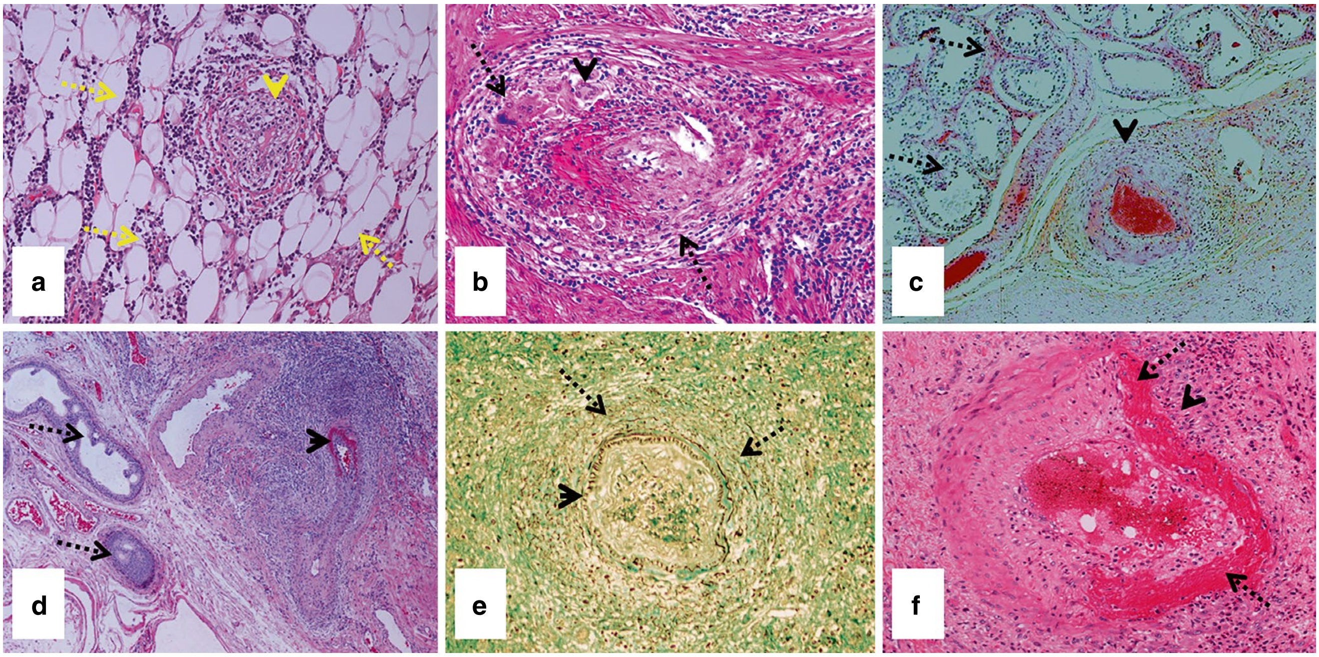

Fig. 29.3 Histological features in five patients with focal single-organ vasculitis (SOV) and one patient with systemic vasculitis. (**a**) Breast SOV with necrotizing medium-sized arteritis (short arrow) surrounded by mild inflammatory infiltrate in fat tissue (mastitis); (**b**) Granulomatous vasculitis affecting medium-sized vessels of the ovary, disruption of the muscular layer (dashed arrows), and giant cells (short arrow) in a patient finally diagnosed with giant cell arteritis; (**c**) Testicular SOV with non-granulomatous inflammation of a medium-sized artery, and damaged seminiferous tubules (dashed arrows); (**d**) Isolated necrotizing vasculitis with fibrinoid necrosis (short arrow) of the epididymis (different segments marked with dashed arrows); (**e**) Prostatic SOV with artery disruption of the internal elastic lamina (short arrow) and muscular fibers (dashed arrows); (**f**) Gallbladder SOV with necrotizing arteritis showing inflammatory cells within a disrupted muscular layer (short arrow) and fibrinoid necrosis (dashed arrows). Samples A to D and F were stained with hematoxylin-eosin, and sample E with Masson's trichrome stain. Magnification **a**, **c** and **d** × 200; and **b**, **e**, and **f** × 400

administrated to women with systemic vasculitis [7]. Among systemic vasculitides, breast vasculitis has been more frequently associated with GPA. In such patients, classical GPA features usually precede the occurrence of mammary lesions. PAN and GCA with breast involvement have been less frequently reported [7].

Gynecologic Vasculitis

All female genital structures (ovaries, fallopian tubes, uterus, vagina, and vulva) may be affected by systemic vasculitis and SOV. The unexpected incidence of vasculitis among gynecologic surgeries in two large series is of 0.04% and 0.15% [10, 13]. A retrospective literature review analyzing 163 patients with gynecologic vasculitis (115 SOV and 48 systemic vasculitis) provided valuable information about gynecologic SOV [10]. Clinical manifestations leading to a diagnosis of gynecologic vasculitis included vaginal bleeding as the most frequent abnormality, followed by asymptomatic abdominal masses, uterine prolapse, atypical cervical smear, and pelvic pain [10]. Vasculitis was the only lesion in about a third of the resected specimens, and the remaining two third of patients presented with a wide range of concomitant benign and malignant lesions [10]. Among them, the most common benign lesions concomitantly found with vasculitis were leiomyomas, and endometrial carcinoma was the most prevalent malignant lesion [10]. Only benign ovarian abnormalities were more frequently observed in systemic vasculitis than in SOV [10].

Several clinical, laboratory, and histopathologic features in patients with gynecologic vasculitis contribute in distinguishing disease extent [10]. Women with SOV tend to be younger than those with systemic vasculitis (median age 51 vs. 68 years). However, the overlapping age ranges in both groups make age not a reliable distinctive feature in clinical practice. Compared with systemic vasculitis, patients with gynecologic SOV present less often with fever, constitutional/musculoskeletal symptoms, elevated ESR, and anemia. Regarding local presentation, patients with SOV suffer more frequently vaginal bleeding (57% vs. 25%). However, asymptomatic pelvic masses are more commonly observed in women with systemic vasculitis (6% vs. 35%) [10]. While the uterus, and particularly the cervix, are more frequently affected as focal lesions, multifocal lesions tend to settle in different areas in systemic forms, being ovaries, fallopian tubes, and myometrium the territories more frequently affected [10].

Histopathology of gynecologic vasculitis is characterized by a similar involvement of medium and small vessels in both systemic and SOV forms [10]. However, granulomatous vasculitis has been described in two-thirds of patients with systemic vasculitis (Fig. 29.3b), and non-granulomatous inflammatory pattern in >90% of patients with SOV [10].

Gynecologic SOV lesions are usually cured after excisional surgery and do not require pharmacological treatment [10]. Indeed, in patients with cervix SOV discovered in incisional biopsies, vasculitis lesions do not spread distantly even with an incomplete resection and without receiving targeted systemic therapy [10]. However, gynecologic involvement as part of a systemic vasculitis always requires glucocorticoids, and occasionally, additional immunosuppressive therapy [10].

Gynecologic involvement in systemic vasculitides has been most commonly reported in GCA, followed by PAN and GPA, and less frequently by MPA, cryoglobulinemic vasculitis, and vasculitis associated with rheumatoid arthritis and systemic lupus erythematosus [10]. Special mention requires gynecologic vasculitis in GCA, since up to a third of patients with GCA discovered after an abnormal gynecologic biopsy presented as a silent form without classic GCA manifestations [10]. Consequently, the incidental discovery of a pelvic mass displaying granulomatous vasculitis in women >50 years always warrants an exhaustive screening searching for systemic vasculitis, especially GCA [10].

The vagina and vulva have been sporadically reported as SOV. Particularly, vasculitis in the vulva has been associated with Epstein-Barr virus, Behçet disease, GPA, and rheumatoid vasculitis [3].

Vasculitis of Male Genital Structures

Male genital tract comprises testicles, epididymis, vas deferens, spermatic cords, seminal vesicles, prostate, and penis. All these structures may be affected by vasculitis, either as focal SOV or as part of a systemic vasculitis [11]. Vasculitis involving the testicles and vicinity structures are usually manifested with situations resembling testicular tumor, local infection, or spermatic cord torsion. The unexpected finding of vasculitis in all testicular surgeries accounts for 0.003% of the procedures [11].

A review of 72 patients with testicular vasculitis (37 SOV and 35 systemic vasculitis) revealed that the most frequent presentation was a painful testicular mass or enlarged testicle (75% of patients) [11]. Other manifestations included painless masses or swelling affecting testicles or epididymis, with bilateral involvement in 15% of cases. In both SOV and systemic disease, vasculitic lesions occur isolated or multifocal (in different testicular structures). Among male genital structures, vasculitis affects testicles in 80% of cases (Fig. 29.3c), followed by epididymis (45%) (Fig. 29.3d) and vas deferens/spermatic cord (31%) [11]. Testicular vasculitis is confirmed more often by orchiectomy, followed by biopsies of testicles, epididymis, and spermatic cord [11].

Compared to patients with systemic vasculitis, those with SOV present less often with fever, constitutional and/or musculoskeletal symptoms, elevated ESR, and anemia. Other features, such as patients' age, local manifestations, and their duration until diagnosis, as well as the testicular sites affected, and the extent as focal or multifocal vasculitis did not differ between the two groups [11].

Regarding histopathology, non-granulomatous medium-vessel vasculitis are the predominant lesions found in most patients with either testicular SOV and systemic vasculitis [11]. Simultaneously with vasculitis lesions, testicular carcinoma has been the only reported lesion in about 5% of SOV patients [11]. As occurring in gynecologic SOV, concomitant testicular lesions potentially triggering isolated vasculitis have not been found associated to any of the two vasculitis forms [11].

Because malignant lesions are more frequently suspected in SOV than in systemic vasculitis, patients with testicular SOV are most often diagnosed by orchiectomy and less often by testicular biopsy than patients with systemic vasculitis [11]. Testicular SOV is usually managed with surgery alone, and systemic vasculitis with glucocorticoids and additional immunosuppressive drugs [11].

PAN and hepatitis B virus (HBV)-associated vasculitis are the most frequent systemic vasculitides with testicular involvement, accounting in two-thirds of all the reported cases [11]. In this regard, although overt testicular symptoms are manifested by <20% of patients with PAN, genital vasculitic lesions have been observed in almost all PAN cases at necropsy examination [3]. Other systemic vasculitides with testicular involvement include GPA, immunoglobulin A (IgA) vasculitis, MPA, cryoglobulinemic vasculitis, GCA, and eosinophilic granulomatosis with polyangiitis (EGPA) [11]. Recently, testicular involvement has been also described in patients with deficiency of adenosine deaminase 2 (DADA2) and vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome, two monogenic autoinflammatory diseases clinically resembling PAN, and caused by germinal and post-zygotic mutations, respectively [3, 14].

Prostate SOV has been reported as lymphocytic vasculitis affecting small to medium-sized arteries in 12.4% of samples from a surgical series of 540 patients with benign prostatic hyperplasia. The isolated nature of vasculitis was confirmed since surgical excision was the only therapeutic intervention in all patients [3]. Prostate SOV has also been reported in several patients presenting with urinary obstruction or prostatitis. In such cases, biopsies revealed prostatic granulomatous vasculitis with eosinophilic infiltrates or necrotizing arteritis (Fig. 29.3e), and glucocorticoids were used to resolve local symptoms [3]. GPA is the systemic vasculitis more frequently affecting the prostate, followed by MPA, EGPA, PAN, and HBV-associated vasculitis [3]. Apart from systemic immunosuppressive therapy, some patients, mainly those with GPA, may require prostate surgery [3].

SOV of the seminal vesicles has been detected after radical prostatectomy in two patients accompanying prostate adenocarcinoma [3]. While only one case of penis SOV has been reported, most cases of penile vasculitis have been associated with systemic vasculitides, mainly GPA, and less often PAN, IgA vasculitis, lupus-associated vasculitis, Behçet disease, and Buerger's disease. Penile resection was performed in some patients, but most cases required immunosuppressive therapy [3].

Ureter, urinary bladder, and urethra are segments of the urinary tract that, although infrequent, may be affected by systemic vasculitides [3]. The unexpected discovery as SOV in these urinary structures, usually mimicking localized tumors, has been seldom reported. However, some of them, mainly those with bladder and urethral vasculitis, cannot be consistently considered isolated since patients were treated with glucocorticoids alone or combined with cytotoxic drugs. Overall, vasculitic lesions affecting the urinary tract, either as SOV or as part of a systemic vasculitis, are usually associated with significant risk of local strictures and/or damage, obstructive hydronephrosis, and secondary renal failure [3]. Among systemic vasculitides affecting the urinary tract, GPA is by far the most frequent, followed by isolated cases of PAN, EGPA, IgA vasculitis, and Behçet disease [3].

Vasculitis of Abdominal Structures

Abdominal territories are frequently involved in systemic vasculitis, mainly in PAN, but also in GPA, MPA, EGPA, IgA vasculitis, Behçet's disease, Takayasu's arteritis, GCA, and chronic periaortitis or IgG4-related disease [2, 8, 9]. Abdominal SOV has been occasionally described affecting gallbladder, esophagus, stomach, omentum, small and large intestine, appendix, and pancreas. SOV localized in the esophagus, stomach, and omentum has been reported to resolve with surgical excision alone, but complications of gastrointestinal vasculitis, mainly of those affecting the small or large bowel, entails a higher morbidity and mortality risk, independently of whether vasculitic lesions are part of systemic vasculitis or SOV. Although several cases of SOV involving the small bowel and colon have been cured by surgical resection alone, most of the cases diagnosed with intestinal SOV received systemic immunosuppressive therapy [2, 9].

The appendix may be involved in different systemic vasculitides, but mainly in PAN, since vasculitis of the appendix occurs in about 10% of patients with PAN [2]. However, the appendix is the most common site in which SOV has been described to occur, since the prevalence of vasculitis in appendectomies because of local symptoms or other unrelated surgeries in which appendix is simultaneously removed, is similarly of 1.2–1.3%. Patients with an initial appendix SOV do not require systemic treatment during long-term follow-up [2].

Gallbladder vasculitis has been reported as SOV or as part of a systemic vasculitis [2, 8]. Vasculitis has been observed in 0.04% to 0.29% of the cholecystectomies performed for cholecystitis or complicated cholelithiasis [8]. Among systemic vasculitis, gallbladder vasculitis has been described in 8–40% of patients with PAN and in less than 2% of patients with other vasculitis and autoimmune diseases [8]. In a review of 61 patients with gallbladder vasculitis (20 SOV and 41 systemic vasculitis), no differences were observed in age, gender, or duration of local symptoms between groups. While lithiasic cholecystitis was more frequent in patients with SOV, acalculous cholecystitis occurred more often in those with systemic disease. Constitutional and musculoskeletal symptoms were reported only in patients with systemic vasculitis. Fever and higher ESR levels predominated in patients with systemic extent [8]. All patients with systemic vasculitis received systemic glucocorticoids and additional immunosuppressive drugs. Mortality was higher in patients with systemic vasculitis. Histopathology did not discriminate between disease extent since non-granulomatous inflammation with fibrinoid necrosis of medium-sized vessels (Fig. 29.3f) occurred equally in >90% of patients in both groups [8]. Systemic vasculitides most frequently affecting the gallbladder included PAN, HBV-associated vasculitis, and cryoglobulinemic (essential or HCV-associated) vasculitis. Less frequently, vasculitis associated with autoimmune diseases, MPA, EGPA, IgA vasculitis, and GCA were also reported [8].

Systemic vasculitis with pancreas involvement is rare (<1%). Pancreas SOV has been reported with acute or chronic abdominal pain, and imaging revealed inflammation of the entire pancreas or a mass lesion mimicking neoplasm. Resection of pancreatic lesions has been curative in these cases [2, 9].

Diffuse Single Organ Vasculitis

Primary Central Nervous System Vasculitis

Primary CNS vasculitis, or primary angiitis of the CNS, is a diffuse SOV affecting CNS structures. Neurological manifestations are characterized by headache, focal, and/or cognitive deficits not attributable to common identifiable causes. Cerebral angiography imaging and/or CNS histology should evidence changes suggestive of vasculitis (Fig. 29.4). However, the exclusion of systemic vasculitis involving CNS or other conditions simulating angiographic and histological findings of vasculitis is mandatory. Diagnostic criteria were coined by Calabrese and Mallek in 1988 (Table 29.1) and have been profusely used in clinical investigation [15]. Recent progresses have been made in neuroimaging techniques contributing in differentiating inflammatory from noninflammatory vasculopathies, and molecular technologies contributing to identify infectious signals and genetic causes of CNS vasculitis [16].

Although isolated, primary CNS vasculitis is often a severe form of vasculitis associated with high morbidity and mortality, and frequently requires glucocorticoids at high doses, usually accompanied by cyclophosphamide or rituximab [15, 17].

Cutaneous Leukocytoclastic Angiitis

CLA, previously known as cutaneous leukocytoclastic vasculitis, affects small-sized blood vessels, usually postcapillary venules, in the superficial dermis. CLA is clinically manifested as petechiae and palpable purpura. Isolated cases are usually self-limited. CLA is the most common cutaneous vasculitis form, since it may be the expression of primary and secondary immune reactions mediated by circulating immune complexes. Although the underlying cause of CLA remains unknown in about half of cases, secondary immune complex small vessel vasculitides include those triggered by infections, reactions to medications, or neoplasms, and also those associated with systemic vasculitides and other autoimmune diseases [12].

Among infections, CLA has been recently reported to occur in both SARS-CoV-2-infected and SARS-CoV-2-vaccinated patients. Most of these subjects suffer spontaneous self-limiting cutaneous forms without systemic involvement, and others improve after systemic treatment [18]. Systemic small-vessel vasculitides that can manifest with CLA include ANCA-associated vasculitis (GPA, MPA, and EGPA), and immune-complex vasculitis (IgA vasculitis, cryoglobulinemic vasculitis, hypocomplementemic urticarial vasculitis, and vasculitis associated with infectious agents) [12]. The therapeutic approach of CLA should be tailored depending on disease extent, severity, and recurrences.

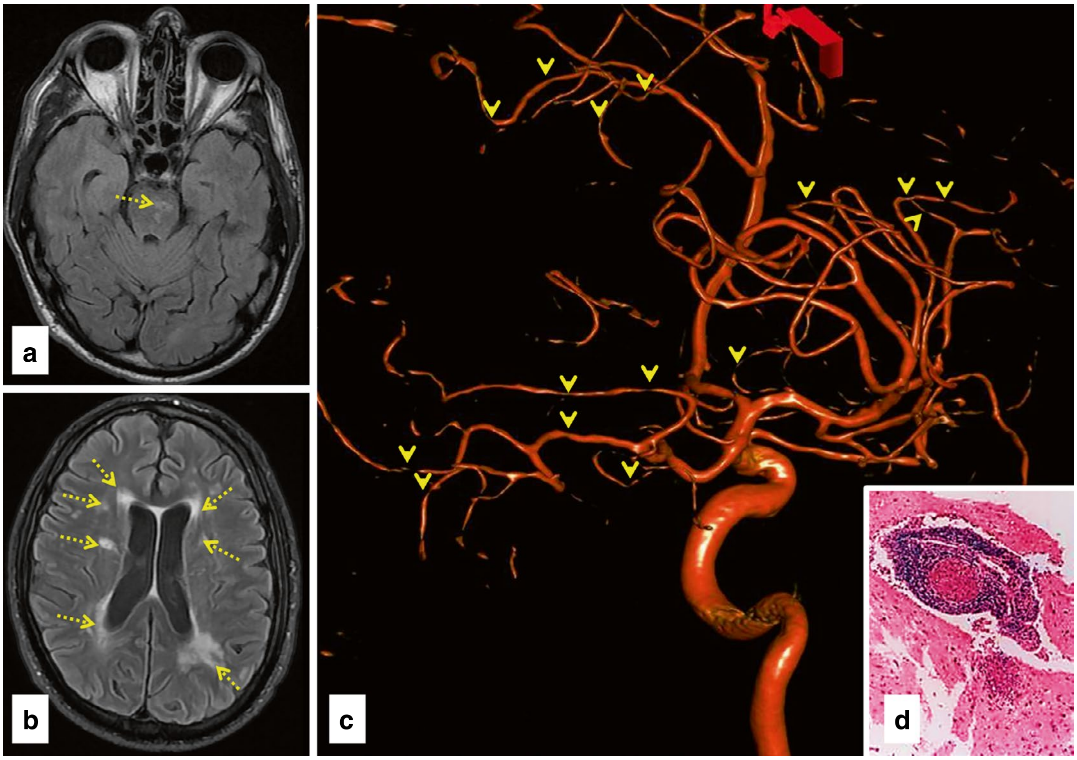

Fig. 29.4 Primary isolated central nervous system angiitis. (**a**) Brain magnetic resonance showing ischemic lesions in cerebral trunk (arrow) and (**b**) multiple periventricular, subcortical, and basal ganglia (arrows) (**b**); (**c**) 3D reconstruction of catheter-directed angiography showing numerous stenoses at different levels (short arrows) and post-stenotic dilations; (**d**) Brain biopsy revealing medium-caliber artery with necrotizing vasculitis and transmural lymphocyte inflammation (**d**)

Table 29.1 Diagnostic criteria for primary central nervous system (CNS) angiitis [15]

1	The presence of an acquired otherwise unexplained neurological or psychiatric deficit
2	The presence of either classic angiographic or histopathological features of angiitis within the CNS
3	No evidence of systemic vasculitis or any disorder that could cause or mimic the angiographic or pathological features of the disease[a]

[a]The authors emphasize the necessity of exclusion of involvement of CNS by systemic vasculitides and CNS vasculitis mimics before the diagnosis of primary CNS angiitis is established

Cutaneous Arteritis

Cutaneous arteritis is a medium-sized vessel vasculitis exclusively affecting the skin. The 2012 CHCC recommended the use of the term of cutaneous arteritis instead of cutaneous PAN, and differentiated it from CLA as two cutaneous SOV forms [1]. However, the 2018 dermatologic addendum of 2012 CHCC for nomenclature of cutaneous vasculitis allowed again to called cutaneous arteritis as "cutaneous PAN" [19]. Its etiology remains unclear. Cutaneous arteritis is characterized by multiple painful reddish tender nodules, livedo reticularis or racemosa, and ulcerative lesions, and less frequently atrophie blanche and purpura [12]. Lesions are usually relapsing and localized in lower limbs in most cases. Because the nerves and muscles can be affected by proximity underlying the affected skin, myalgia, neuropathic symptoms, arthralgia, fever and constitutional involvement is observed in a variable proportion of patients [12]. Therapeutic options in cutaneous arteritis depend on disease severity and the occurrence of relapses, and range from conservative measures in mild cases, to high-doses of glucocorticoid and additional immunosuppressive drugs in relapsing or severe forms [12].

Other Cutaneous Single-Organ Vasculitis

The 2018 dermatologic addendum of 2012 CHCC for nomenclature of cutaneous vasculitis distinguished new forms of cutaneous single-organ vasculitis, such as cutaneous IgM/IgG immune complex vasculitis, nodular vasculitis (or erythema induratum of Bazin), erythema elevatum et diutinum, recurrent macular vasculitis in hypergammaglobulinemia (or hypergammaglobulinemic purpura of Waldenström), and normocomplementemic urticarial vasculitis [19].

Isolated Retinal Vasculitis

SOV or isolated retinal vasculitis is a primary or idiopathic sight-threatening inflammatory condition confined to the retinal vessels, accounting for 6% of all cases of retinal vasculitis [20]. Retinal SOV is considered a posterior uveitis generally affecting adult women, often with bilateral involvement and retinal phlebitis. Visual loss is frequent and severe in 27% of patients. Treatments used include systemic glucocorticoids in most patients, but despite systemic immunosuppressive medications and intensive local procedures, mainly intravitreal therapy and panretinal photocoagulation, visual improvement is observed in only a quarter of patients [20].

Retinal vasculitis is more frequently associated with other diseases, such as infections (e.g., herpes viruses, cytomegalovirus, toxoplasmosis, tuberculosis, toxocariasis, syphilis, Lyme disease), cancer (e.g., ocular lymphoma, acute leukemia, and paraneoplastic syndromes secondary to solid tumors), or systemic or organ-specific autoimmune diseases, most commonly Behçet's disease and sarcoidosis, followed by other systemic vasculitides (e.g. GPA, PAN, EGPA), and relapsing polychondritis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis. Retinal vasculitis may be also part of isolated ocular syndromes, such as pars planitis, Birdshot choroidopathy, Vogt-Koyanagi-Harada disease, Fuchs uveitis syndrome, and IRVAN (idiopathic retinal vasculitis, aneurysms, and neuroretinitis) syndrome, Eales disease (retinal periphlebitis with superficial hemorrhages), Frosted branch angiitis, and acute multifocal hemorrhagic retinal vasculitis, and others [2, 20].

Conclusions

Single-organ vasculitis (SOV) is a category of vasculitis adopted at the 2012 CHCC on the nomenclature of vasculitides that encompasses a group of diseases in which vasculitic involvement is confined to a specific organ, system, or territory. SOV may be divided in focal diffuse forms. Focal SOV are usually incidentally found in evaluations for malignant or infectious conditions. In focal SOV, the resection of the inflammatory lesion may lend to the resolution of the inflammatory process. Diffuse SOV usually required systemic immunosuppressive or immunomodulatory therapy. Anyway, a definite diagnosis of SOV always requires excluding a systemic illness and also reassuring that isolated vasculitis is not a limited expression of a systemic disease. Except for some forms of aortic, gastrointestinal, or urologic SOV, which can be associated with local rupture or obstruction with severe of fatal consequences, often requiring additional surgical management, the prognosis of focal SOV in other locations is usually satisfactory. In some focal SOV forms, certain clinical, laboratory, and histopathologic features may contribute in distinguishing isolated from systemic vasculitis, and subsequently, in using guided diagnostic and therapeutic strategies.

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Part III

Idiopathic Inflammatory Myopathies

Polymyositis

30

Gema M. Lledó-Ibáñez, Jorge Álvarez Troncoso,
and Sergio Prieto-González

Abstract

Polymyositis represents one of the classical major forms of idiopathic inflammatory myopathies (IIM). Its prevalence is not known because of overdiagnosed cases, especially muscular dystrophies and inclusion body myositis (IBM). PM usually presents in middle age, particularly in women. Pathogenic mechanisms include the abnormal expression of major histocompatibility complex (MHC)-class I antigens and the activation of CD8 cells. The clinical pattern consists in a subacute or chronic proximal muscle weakness, with an increment of serum CK values. In contrast to dermatomyositis, cancer risk is very low. PM may be associated with other autoimmune and infectious diseases. In most cases, a satisfactory clinical response can be obtained with corticosteroids and immunosuppressive agents.

Keywords

Myositis · Polymyositis · Dystrophy · Idiopathic inflammatory myopathies

Introduction

Although the term polymyositis (PM) was first introduced by Wagner in 1863, the recognition of PM as a distinct entity was due to Walton and Adams in 1958. In 1975, these observations were confirmed by Bohan and Peter, and the diagnostic criteria for PM and dermatomyositis were established, still remaining in use today, at least partially [1–3].

PM presents as a myopathy with proximal and often symmetric muscle weakness but without unique clinical features. Its diagnosis requires a careful review of the neurologic examination, muscle histopathology, immunopathology, and biochemistry to ensure that a toxic, metabolic, or mitochondrial muscle disease, or alternative IIM, such as immune-mediated necrotizing myopathy or inclusion body myositis, are not overlooked.

Epidemiology

Once considered the most common idiopathic inflammatory myopathy (IIM), PM is almost extinct now. Moreover, PM is often overdiagnosed or misdiagnosed, and nowadays is considered as a diagnosis of exclusion so incidence and prevalence of PM is unknown [4].

Pathogenesis

Physical, chemical, or external infectious agents may act upon a genetically predisposed person. The relationship of PM with other autoimmune disorders, the existence of autoantibodies, histocompatibility genes, the presence of T cells in muscle tissue and their response to immunotherapies, has led PM to be considered an autoimmune disease, but no specific target antigens have been identified yet. The PM pattern is characterized by endomysial inflammatory infiltrates of activated CD8 T lymphocytes and macrophages. The CD8 cytotoxic T lymphocytes recognize the major histocompatibility complex class I (MHC-I) expressed on muscle fibers and invade non-necrotic muscle cells inducing necrosis through the perforin pathway [5].

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Clinical Manifestations

Muscle involvement usually develops over the course of weeks or months. It is characterized by symmetrical and proximal limb weakness, affecting the quality of the patient's daily activity. Facial muscles remain unaffected and distal muscles may be affected only in late stages of the disease as may paravertebral muscles, leading to the camptocormia syndrome. Involvement of neck muscles is rare, but if present, dropped head is the principle sign.

Extramuscular involvement is more common in other types of IIM, but may also occur in PM. Joint manifestations may occur even without an association with other autoimmune diseases. They are characterized by arthralgia and nonerosive arthritis involving the wrists, knees, and the small joints of the hands. Cardiac involvement varies widely between 6% and 75%, depending on whether clinical events or subclinical manifestations are considered. Clinically, symptomatic cardiac involvement is relatively rare. Cardiac manifestations include arrhythmia, conduction abnormalities, cardiac arrest, congestive heart failure (CHF), myocarditis, pericarditis, valvular heart disease and secondary fibrosis.

As mentioned, PM remains a diagnosis of exclusion. PM as a stand-alone entity is uncommon (Table 30.1).

Table 30.1 Features that the PM patient does not have

Rash (characteristic of dermatomyositis)
Family history of neuromuscular diseases
Exposure to myotoxic drugs, especially penicillamine, zidovudine, and (rarely) statins
Endocrine disease (hypothyroidism, hyperthyroidism, hypoparathyroidism, hypercortisolism)
Neurogenic disease (exclude by electromyography and neurological examination)
Dystrophies[a] and metabolic myopathies (excluded by history and muscle biopsy)
Inclusion body myositis (excluded by clinical examination and muscle biopsy)

[a] Dysferlin deficiency and facioscapulohumeral muscular dystrophies in particular because severe inflammation can be found in muscle biopsies

Pathology

Muscle biopsy is the definitive examination for the diagnosis. Findings include endomysial inflammatory infiltrates consisting predominantly of CD8-T cells that invade healthy muscle fibers (Fig. 30.1) expressing the MHC-I antigen, which is ubiquitously upregulated on the surface of most fibers. The MHC/DC8 complex is characteristic of PM. Muscle fiber necrosis can be observed as well as regenerating muscle cells. The combination of such pathological data is known as a PM pattern (Table 30.2).

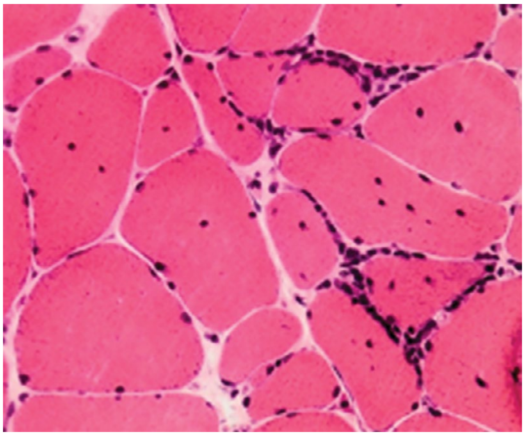

Fig. 30.1 The histological PM pattern: H&E stained, endomysial inflammation invading healthy muscle fibres

Table 30.2 Comparison of different polymyositis definitions. Table adapted from the article by Leclair V, et al. [10]

Authors	Myopathic muscle weakness	Elevated muscle enzymes	Myopathic EMG	Other features	Histopathology
Bohan and Peters [2, 3]	X	X	X	–	Necrosis, phagocytosis, regeneration with basophilia, large vesicular sarcolemmal nuclei and prominent nucleoli, perifascicular atrophy, variation in fiber size, and inflammatory exudate often perivascular
Dalakas [1, 5, 6, 13]	X	X	X	–	Primary inflammation with CD8/MHC1 complex and no vacuoles OR ubiquitous MHC-1 expression but no CD8-positive infiltrates or vacuoles
Van der Meulen [14]	X	X	–	–	Mononuclear cells surrounding and preferably invading individual nonnecrotic muscle fibers in the endomysium
Tanimoto [15]	X	x	X	Anti-Jo1 Overlap feature[a]	Inflammatory infiltration with degeneration or necrosis of muscle fibers, active phagocytosis, central nuclei, or evidence of active regeneration
ENMC criteria [16]	X	x	X	–	Endomysial inflammatory T cell infiltrate surrounding and invading nonnecrotic muscle fibers OR endomysial CD8 T cells surrounding, but not definitely invading nonnecrotic muscle fibers, or ubiquitous MHC-1 expression

(continued)

Table 30.2 (continued)

Authors	Myopathic muscle weakness	Elevated muscle enzymes	Myopathic EMG	Other features	Histopathology
EULAR/ACR [17]	X	x	X	Anti-Jo1 Overlap feature[a]	Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers

[a] Fever, arthralgias/arthritis

Diagnosis

PM diagnosis necessitates a confluence of clinical manifestations and supplementary tests for validation, encompassing serum muscle enzyme concentrations, electromyography, diverse modalities in muscle imaging, such as Magnetic Resonance Imaging (MRI), Ultrasonography (US), and Positron Emission Tomography (PET), alongside the definitive tool of muscle biopsy. The latter method currently holds the mantle of the gold standard.

Predominantly, the serum muscle enzyme that garners focus is creatine kinase (CK), with levels escalating up to 50 times the norm. While other enzymes like aspartate and alanine aminotransferases, lactate dehydrogenase, and aldolase might register elevations, CK consistently exhibits augmentation in patients displaying active disease [6].

Electromyography unveils a myopathic process characterized by amplified spontaneous activity, featuring fibrillations, complex repetitive discharges, and positive sharp waves [6].

Turning to imaging techniques, MRI presently reigns as the premier modality for skeletal muscle evaluation, providing insightful characterization of muscle edema and fat substitution through T1-weighted and T2-weighted fat-suppressed/STIR sequences. While qualitative assessment of MRI abnormalities is feasible, a quantitative approach, employing Dixon sequences and water T2 parametric maps, emerges as the preferable choice for follow-up. Modern protocols involving diffusion-weighted imaging, functional imaging metrics, and spectroscopy bear potential to further unravel myositis intricacies. Despite MRI's advantages, its image acquisition demands substantial time and financial investment, rendering it inaccessible for all patients [7].

Ultrasonography gains prominence as an avenue to assess skeletal muscle in myositis, particularly in chronic cases where fat replacement and fibrosis are readily detectable. Yet, its effective deployment rests heavily upon operator expertise in recognizing disease states. Moreover, there exists a compelling need for systematic characterization of muscle edema through US [7].

PET emerges as a valuable tool, furnishing insights into muscle function at the cellular level. Fluorodeoxyglucose-PET (FDG-PET) finds prolific application in myositis, detecting pathological uptake indicative of inflammation. Beyond this, neurodegenerative markers now find utility, notably in the case of inclusion body myositis. These disparate modalities, poised as complementary approaches, hold promise for a comprehensive evaluation of myositis [7].

Diagnostic Criteria

The term "polymyositis" emerged within the scientific literature around 1860, serving to characterize a disorder characterized by weakness in skeletal muscles and observable abnormalities in muscle fibers through early microscopes [8]. In 1863, instances emerged of patients presenting with a similar clinical profile but distinguished by a notable skin rash, prompting the designation of their condition as "dermatomyositis" [9]. In the subsequent years, "polymyositis" encompassed a spectrum of disorders, often used interchangeably with "dermatomyositis," irrespective of the presence of concurrent skin rash [10].

Moving ahead to 1958, Walton and Adams undertook a systematic endeavor to craft a more precise definition of PM [11]. They outlined distinct clinical attributes of IIM, including muscular weakness in limb girdles, pain, arthralgias, fevers, and the potential for overlaps with connective tissue disorders, such as systemic lupus erythematosus, systemic sclerosis, and rheumatoid arthritis. The pivotal role of muscle biopsies in the clinical assessment of IIM patients was underscored, although they acknowledged that histopathological changes in PM could manifest in discrete and nonspecific forms [12]. During this era, the differentiation between PM and DM rested on the presence or absence of skin rashes, a distinction mirrored in the diagnostic and classification criteria proposed by Bohan and Peter in 1975 [2–3**].** Subsequent to these developments, diverse IIM classification criteria emerged, incorporating polymyositis as a subset, each harboring unique definitions (Table 30.2) [1, 2, 3, 5, 13–17].

Subsequent to the release of the 2017 EULAR/ACR classification criteria, numerous cohorts undertook assessments of their performance, affirming their heightened sensitivity in identifying IIM [17]. However, **Loarce-Martos et al.** [18] discovered that within their IIM cohort, encompassing 255 patients, a mere 37 were classified as polymyositis according to the 2017 EULAR/ACR criteria and only nine of these cases maintained their designation as polymyositis, all of which were seronegative. The remaining cases were subsequently reclassified into distinct entities, including dermatomyositis, cancer-associated myopathy, immune-mediated necrotizing myopathy, connective tissue disease-associated myopathy, among others.

Serological Features

Recent breakthroughs in the realm of autoantibodies and histopathology have brought about a significant paradigm shift in the traditional classification of IIM, ushering in more refined diagnostic and categorization strategies.

The presentation of antisynthetase syndrome, beyond the presence of specific antibodies (antibody against histidyl-tRNA synthetase [ARS]), encompasses interstitial lung disease (ILD), arthritis, Raynaud's phenomenon, mechanic's hands, and systemic symptoms. Muscle biopsies commonly exhibit perifascicular necrosis and perimysial fragmentation, distinguishing it from the conventional PM. In contrast, immune-mediated necrotizing myopathy is characterized by severe muscle disease, frequently marked by predominant necrosis in biopsies, alongside cases featuring lymphocytic infiltrates. In such instances, the presence of autoantibodies associated with immune-mediated necrotizing myopathies, such as signal recognition particle (SRP) or 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR), serves as a decisive factor in excluding the diagnosis of polymyositis. Likewise, overlap myositis, linked with autoantibodies like anti-RNP, anti-Ku, or anti-PM/Scl, results in varying diagnoses contingent upon the clinical context [10].

However, patients lacking specific autoantibodies frequently receive a diagnosis of PM. Nevertheless, the accurate diagnosis of PM necessitates the careful exclusion of alternative conditions, including IBM or noninflammatory disorders. Employing advanced imaging techniques aids in differentiation, and the absence of an immunosuppressive response may hint at an alternative diagnosis.

Finally, it is mandatory to pay due attention to immune checkpoint inhibitor-associated myopathy, a condition that sometimes presents with discrete inflammatory infiltrates similar to patterns seen in immune-mediated necrotizing myopathies. However, recent investigations posit that the hallmark of this entity lies in the presence of multifocal clusters of necrotic fibers. Within this context, considering their frequent lack of association with specific antibodies, and despite certain similarities between immune checkpoint inhibitor-associated myopathy and PM, the distinct clinical manifestations and characteristic histopathological attributes, reminiscent of immune-mediated necrotizing myopathies, preclude its classification as a mere "model" of polymyositis. Rather, it substantiates its status as a unique and discrete entity [19].

Treatment

PM is an IIM that needs a carefully tailored and individualized treatment approach. Before initiating treatment for PM, it is essential to conduct a thorough differential diagnosis, particularly to distinguish it from muscular dystrophies where immunosuppressive therapy and corticosteroids may be ineffective or even deleterious.

The initial treatment in PM typically involves high-dose glucocorticoids. While effective in controlling inflammation, the efficacy of corticosteroids alone has not been extensively validated in randomized controlled trials, and some patients may not respond favorably.

To avoid damage accrual and minimize the undesirable side effects of steroids, it is advisable to combine corticosteroids with second-line agents from the beginning of the treatment. This steroid-sparing approach often includes immunosuppressives, such as methotrexate and azathioprine. Intravenous immunoglobulin (IVIG) may also be considered, particularly as a second-line treatment [5].

In cases where initial treatments are ineffective or if the disease presents with severe muscular or extramuscular manifestations, other therapeutic options may be explored. These include mycophenolate, tacrolimus, cyclophosphamide, and rituximab [20]. Other options like abatacept and tofacitinib may be useful in selected cases. Multi-target treatment strategies have shown promise in refractory cases, further emphasizing the need for a multifaceted approach.

Despite the availability of these treatment options, outcomes can still be unsatisfactory, and no single drug or combination has been universally effective in treating certain complications.

In addition to pharmacological interventions, the evidence suggests that exercise therapy could be a beneficial addition to medical treatment for polymyositis, but more research is needed to determine the best protocols.

The treatment of polymyositis must be thoughtfully tailored to each patient, taking into account factors such as disease severity, response to previous treatments, and comorbidities. Regular follow-up with a specialist in autoimmune disorders is essential for monitoring disease progression and making necessary adjustments to the treatment plan.

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31 Dermatomyositis

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Abstract

Dermatomyositis (DM) is a systemic autoimmune condition characterized by muscle and skin inflammation. Proximal muscle weakness and characteristic skin rashes dominate the clinical picture. However, pulmonary, renal, and esophageal involvements can also be observed.

An increase in serum levels of muscle enzymes and characteristic electromyographic and imaging findings are important in the diagnostic workup and in the follow-up of DM patients, while muscle biopsy remains important especially in patients without specific skin rashes. Myositis-specific antibodies (MSA) are disease-specific markers, which are becoming increasingly central in the diagnosis and management of DM. MSA allow for early recognition of DM even before the onset of clinically overt myositis, allow the identification of homogeneous subgroups of DM patients, and predict treatment response. Notwithstanding their potential, MSA detection is still poorly standardized and expensive. Over the years, several diagnostic and classification criteria have been proposed to aid clinicians and researchers to correctly identify patients with this rare disease. The 2017 EULAR/ACR classification criteria represent the latest effort of the scientific community in this direction, proving to perform better than their predecessors.

Keywords

Dermatomyositis · Idiopathic inflammatory myopathies · Myositis-associated autoantibodies · MSA

Introduction

Idiopathic Inflammatory Myopathies (IIMs) are a heterogeneous group of rare systemic autoimmune conditions characterized by inflammatory muscle damage often coupled with major organ involvement, such as skin, lungs, and gastrointestinal tract. They are typically classified according to relevant clinical, histopathological, and immunological features (Table 31.1).

Dermatomyositis (DM) is an IIM characterized by skeletal muscle and skin involvement. Over the course of the years, it was further subdivided into several subgroups according to the extent of muscle involvement, association with autoimmune and non-autoimmune conditions, and age of onset (Table 31.1). As a consequence, classic DM can be distinguished from Clinically Amyopathic Dermatomyositis (CAMD), where skin disease prevails over muscle involvement, which can be subclinical (hypomyopathic DM) or absent (amyopathic DM/ DM sine myositis), cancer-associated DM (CAM), connective tissue disease (CTD)-overlap myositis (presenting as either polymyositis -PM- and DM), and juvenile DM (JDM). Each subset of DM has shown a predilection for specific manifestations as well as different course, treatment response, and prognosis. However, the ongoing identification of myositis-specific antibodies (MSA) and myositis-associated antibodies (MAA) and their association with DM subtypes has changed this paradigm allowing a new classification system to be introduced in clinical practice (Table 31.1).

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Table 31.1 Classification of IIMs

Standard classification

- Dermatomyositis
  - Classic dermatomyositis
  - Juvenile dermatomyositis
  - Cancer-associated dermatomyositis
  - Connective tissue disease-associated dermatomyositis
  - Clinically amyopathic dermatomyositis
    - Hypo-myopathic dermatomyositis
    - Amyopathic dermatomyositis (DM sine myositis)
- Polymyositis
- Inclusion body myositis
- Immune-mediated necrotizing myositis
- Overlap myositis

Autoantibody-based classification

- Anti-synthetase syndrome
- Anti PM-SCL syndrome
- Immune-Mediated Necrotizing Myositis (IMNM)
  - Anti-SRP IMNM
  - Anti-HMG-CoA reductase IMNM
- Inclusion Body Myositis
  - Anti-cN1A
- Dermatomyositis (DM)
  - Anti-Mi2 DM
  - Anti-SAE DM
  - Anti-MDA5 DM
  - Anti-TIF1γ DM
  - Anti-NXP2 DM

Epidemiology

There are limited and highly heterogeneous data available on DM epidemiology, probably due to the rarity of this condition, regional differences in disease incidence and prevalence, as well as methodological differences among different studies mainly related to the data source and the classification criteria applied. In general, reported incidence and prevalence range from 1.2 to 17 cases per million and 5 to 11 cases per 100,000, respectively [1]. Disease incidence appears to increase with age with a peak around 50–79 years of age for both sexes [2]. DM typically shows a female predominance (ratio 2:1) [1]. In cancer-associated DM male gender prevails and the association between DM and malignancy increases with age and occurs in approximately 30% of cases [1].

Pathogenesis

The pathogenesis of DM is not completely clarified although it is thought to be a multifactorial process involving environmental and infectious stimuli in genetically predisposed individuals eventually leading to a breach of self-tolerance. Ultraviolet radiation, vitamin D deficiency, smoke, and viral infections, such as HIV and HTLV1, seem to play a role in DM pathogenesis [3]. A strong association seems to exist between DM and HLA class II alleles, supporting the idea of a T cell-driven immune response. More interestingly, an association between specific HLA alleles has been found with specific MSA, such as the association between HLA-DRB1*03:01 and anti-Jo1 and anti-Mi2 antibodies or anti HLA-DRB1*01:01/*04:05 and anti-MDA5 antibodies [4]. Increased expression of Type I interferon-inducible proteins in DM patients points to a relevant role played by Type I interferons in the pathogenesis of DM, possibly unveiling new therapeutic targets [5]. Overexpression of certain myositis-related antigens in cancer cells, such as Mi2 and TIF1γ, may represent the antigenic stimulus driving the formation of MSA in CAM [4].

Clinical Manifestations

DM primarily affects skeletal muscles and skin [1]. Muscle involvement may have an acute (days) or a more insidious (weeks to months) onset, manifesting with progressive proximal weakness and, less frequently, myalgia. Patients often complain of difficulty standing up from a sitting position or climbing stairs as well as difficulty in hair combing or raising objects over the head. In more severe cases, involvement of the neck's extensors leads to difficulty in holding up the head (head drop), and compromission of the respiratory and oropharyngeal musculature can lead to dysphagia and ineffective cough reflex. Distal musculature is usually involved later in the disease course. Muscle atrophy can also occur in the late stages in up to 40% of the cases as a result of fibro-fatty substitution of skeletal muscles.

Skin disease is a defying feature of DM and can occur together, precede or follow by several months/years muscle involvement (Fig. 31.1). In CAMD cutaneous manifestations can be the only clinically relevant ones with subclinical, or complete absence of, muscle involvement.

Gottron's papules and Gottron's sign are considered two pathognomonic DM manifestations. Gottron's papules are violaceous/erythematous papules occurring in the dorsal aspects of metacarpophalangeal and interphalangeal (IFP) joints. Gottron's sign indicates the presence of macular violaceous erythema in the dorsal aspect of IFPs, hands, elbows, knees, and medial malleoli. Highly characteristic manifestations include heliotrope rash (periorbital violaceous erythema associated with periorbital edema), V sign, and shawl sign (erythematous rash involving the anterior chest and back and shoulder, respectively). DM skin rashes are photosensitive, being present in photo-exposed areas and worsening after direct sunlight exposure.

Patients with DM can also develop acral lesions, such as periungual erythema, cuticular dystrophia, periungual telangiectasia as well as periungual infarction, and digital ulcers.

Calcinosis cutis can be observed, especially in the pediatric population, manifesting as hard painful subcutaneous nodules, which can lead to considerable discomfort and disability with frequent ulceration and infection. The presence

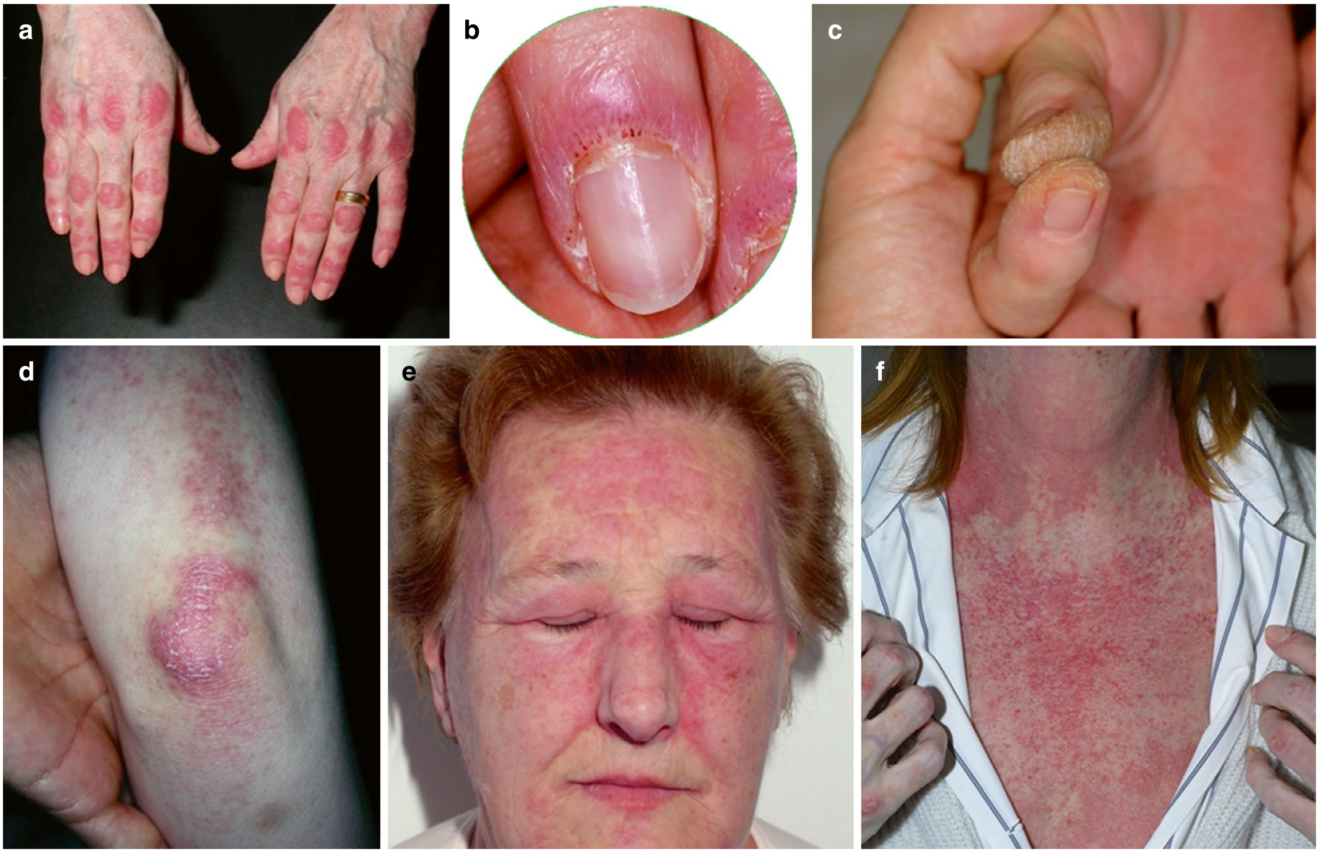

Fig. 31.1 Cutaneous manifestations of dermatomyositis. (**a**) Gottron's papules. (**b**) Periungual erythema, cuticular dystrophia, periungual telangiectasia. (**c**) Mechanic's hands. (**d**) Gottron's sign on the elbow. (**e**) Heliotrope rash with periorbital edema. (**f**) V-sign. This figure was published in "The clinical features, diagnosis and classification of dermatomyositis," Journal of Autoimmunity, Volumes 48–49, February–March 2014, Pages 122–127, Fig. 1. Copyright Elsevier Ltd. (2014)"

of skin thickening and cracking at the level of the fingertips constitute the so-called mechanic's hands, which is typical of Anti-Synthetase Syndrome (ASS) but can be observed in classic DM. Raynaud's phenomenon is common, especially in classic DM, and overlap myositis [1]. Other common manifestations include inflammatory arthralgia/nonerosive arthritis and interstitial lung disease (ILD) [1]. Involvement of cardiac muscle leading to heart failure as well as kidney damage due to glomerulonephritis or myoglobinuria can occasionally be observed [1]. JDM resembles adult DM, although with a higher incidence of subcutaneous calcifications and vasculitic skin changes.

Pathological Features

Histological findings reflect the pathogenic concept of DM as a complement-mediated microangiopathy [6]. Complement activation caused by innate and adaptive stimuli leads to the formation of C5-C9 membrane attack complex (MAC) responsible for endothelial damage and obstructive inflammatory changes in blood vessels. Features typical of DM muscle histology include perivascular inflammation, loss of capillaries, and compensatory telangiectasia of remaining capillaries leading to muscle hypoxic stress and ischemia, particularly at the periphery of the fascicle, ultimately culminating in peri-fascicular atrophy, the characteristic histological feature of DM, which is seen in established ongoing disease. Complement activation also leads to proinflammatory cytokine and chemokine release with tissue infiltration of mainly CD4+ T cells, B cells, macrophages, and plasmacytoid dendritic cells. Skin histology usually shows similar vasculature changes and perivascular inflammatory infiltrates, together with vacuolar changes in the basal cell layer (interface dermatitis) and an increase in dermal mucin [7].

Biomarkers of Muscle Damage

Measurement of blood levels of muscle-derived enzymes or proteins is central in the evaluation of DM and IIMs in general. Creatinine Kinase (CK), aldolase, myoglobin, aspartate and alanine aminotransferase (AST and ALT), and LDH all represent markers of muscle damage used in clinical practice. In particular, CK shows the highest sensitivity [1, 4]. Elevated levels of CK have been long used as a biomarker of DM, fairly correlating with disease activity and allowing the identification of subclinical muscle involvement in hypomyopathic DM. On the other hand, the role of CK as a disease biomarker is hindered by several limitations. Baseline levels of CK vary greatly in the general population potentially affecting the interpretation of measured levels [4]. Moreover, patients with advanced disease might have an active disease with abnormally low CK levels due to extensive muscle atrophy or the presence of inhibitors of CK activity. CK is not useful in the monitoring of patients with amyopathic DM [4].

The search for new biomarkers continues and recent evidence points to the potential role of some MSA in the monitoring of DM, as antibody titers of anti-Jo1 and anti-MDA5, for instance, have been shown to parallel disease activity [4, 8]. Interestingly, studies on anti-MDA5 dermatomyositis have identified ferritin as a good marker of disease course and treatment response, especially in the monitoring of ILD [8].

Autoantibodies

A positive antinuclear antibody test is seen in up to 50% of cases of IIMs using indirect immunofluorescence [1]. The identification of autoantibodies strongly associated with the disease has represented one of the greatest achievements in the field of IIMs.

Over the years the number of autoantibodies associated to IIMs has been growing to the point that today a myositis-related antibody can be identified in approximately 60–70% of patients [4]. Myositis-related antibodies have been historically subdivided into MSA and MAA. MSA are highly specific and often mutually exclusive. These characteristics have allowed segregating DM and IIMs patients into more homogeneous subgroups showing similar clinical manifestations and response to therapies. MAA are not specific to IIMs but are often found in IIM patients, particularly in overlap myositis. DM-associated antibodies are listed in Table 31.2.

Anti-Mi2 and anti-SAE (small ubiquitin-like modifier-1 activating enzyme) antibodies are associated with classic DM. Anti-Mi2 antibodies are usually associated with a more benign disease course and milder muscle involvement with a good response to immunosuppressive therapy. Patients bearing the anti-SAE antibody usually show early skin involvement and develop muscle disease later in the disease course and their presence has been associated with the development of dysphagia. Anti-MDA5 (melanoma-differentiation-associated protein 5) antibodies are usually associated with prominent skin involvement with the typical stigmas of DM

Table 31.2 Myositis-specific antibodies and myositis-associated antibodies in dermatomyositis

Antibody	Target antigen	Clinical association	Frequency in myositis[a]
MSA			
Anti-Mi2	Nucleosome remodeling deacetylase complex	• Classic DM with mild-to-moderate muscle involvement • Good response to therapy • Response to RTX	• Adult: 5–10% • Juvenile: 4–10%
Anti-SAE	Small ubiquitin-like modifier activating enzyme	• Classic DM • Skin disease usually precedes muscle disease • Associated to dysphagia	• Adult: 3% • Juvenile: 1%
Anti-TIF1γ	Transcription intermediary factor 1γ	• Strong association with cancer in adults (>40y) • Typically associated with CADM or DM with mild muscle involvement • In JDM associated with calcinosis	• Adult: 7% • Juvenile: 18–30%
Anti-NXP2	Nuclear matrix protein 2	• Calcinosis in JDM	• Adult: 2–17% • Juvenile: 15–20%
Anti-MDA5	Melanoma differentiation associated protein 5	• CADM • ILD and RP-ILD • Severe skin rash with acral ulcers and calcinosis	• Adult 1–30% • Juvenile 7%
Anti-ARS	tRNA synthetases	• Association with ASS • Sometimes anti-Jo1 is associated with classic DM skin rash • Response to RTX	• Adult 20–30% • Juvenile 2%
MAA			
Anti-PM/SCL 75–100	Exosome (PmScl) complex	• Association of PM/DM with systemic sclerosis and ILD	• Adult 8% • Juvenile 5%
Anti-U1RNP	Small ribonucleoprotein	• Typically associated with mixed CTD	• Adult 10% • Juvenile 5%
Anti-Ro52	TRIM21	• Often associated with ARS and with worse ILD	• Adult 25% • Juvenile 6%
Anti-Ku	Ku complex	• Associated with overlap disease	• Adult <1% • Juvenile <1%

ARS anti-aminoacyl tRNA synthetase, *ASS* anti-synthetase syndrome, *CADM* clinically amyopathic dermatomyositis, *CTD* connective tissue disease, *DM* dermatomyositis, *ILD* interstitial lung disease, *JDM* juvenile dermatomyositis, *PM* polymyositis, *RP-ILDv* rapidly progressive interstitial lung disease, *RTX* rituximab

[a] Percentages are retrieved from reference [10]

and higher incidence of skin calcifications and acral ischemia, mild or no muscle involvement (CADM) coupled with an often-aggressive form of ILD [4]. Anti-TIF1γ (transcription intermediary factor 1 also known as TRIM33) antibodies are strongly linked to malignancy in the adult patient, the strength of such association increases with age. Anti-TIF1γ positive individuals over 40 years of age have up to a 75% chance of having a malignancy [4]. This phenomenon does not seem to be valid for young adults and children where positive anti-TIF1γ is associated with extensive calcinosis. Anti-NXP2 (nuclear matrix protein 2) antibodies are also associated with calcinosis cutis in the pediatric age. Their association with malignancy has not been uniformly demonstrated [4, 9]. Anti-aminoacyl tRNA synthetase (ARS) antibodies are associated with ASS which is characterized by ILD, arthritis, Raynaud's phenomenon, and mechanic's hands [4]. Among the known ARS, anti-Jo1 antibodies represent the first and most common antibody. It is present in up to 19% of adult patients with IIM and, while usually linked to ASS, it has been associated with typical DM skin manifestations [4].

Electromyography/Electroneurography (Emg/Eng)

EMG/ENG represents an easily accessible and low-cost test useful to detect ongoing muscle damage [10].

DM, and IIMs in general, are characterized by muscle membrane irritability leading to fibrillations, positive sharp waves, and complex repetitive discharges in proximal muscles. Motor unit action potentials are small, polyphasic, and recruit early [10].

These findings, however, are not specific to IIMs and are shared among myopathies with cell membrane instability, such as toxic myopathies, muscular dystrophies, myotonic disorders, and myopathies secondary to selected infectious agents, thus requiring a confirmatory muscle biopsy.

Still, EMG/ENG may be particularly useful in the exclusion of myositis mimickers, such as neuromuscular diseases, and can give precious information on the severity and location of damage.

The degree of abnormal muscle membrane irritability parallels the level of IIM activity and decreases as a consequence of muscle atrophy. EMG abnormalities are seen in up to 90% of patients with IIM [1].

Muscle Ultrasonography

Muscle Ultrasound (US) has proven to be a cost-effective method to evaluate muscle inflammation in myositis with good levels of sensitivity [11, 12].

Inflammatory damage is mainly recognized as decreased muscle echogenicity and increased muscle diameter, representing muscle edema. Studies have shown how muscle echogenicity also changes after therapy initiation mirroring disease activity [11]. Fibro-fatty substitution and muscle atrophy can also be recognized as hyperechoic muscle fibers with decreased muscle diameter [12]. Contrast-enhanced ultrasonography (CEUS) has also been applied to study muscle perfusion, showing how active inflammation is associated with increased blood flow to the affected muscles and how blood flow normalizes as muscle inflammation decreases in response to therapy [12].

Although highly practical, US use in IIMs is still limited.

Magnetic Resonance Imaging (MRI)

MRI has become the gold standard among imaging modalities for the study of IIMs [11]. MRI gives a complete and anatomically accurate representation of the ongoing inflammatory process and discriminates it from damage. Short tau inversion recovery (STIR) and T2-weighted images with fat suppression can correctly localize tissue edema and inflammation. Though highly sensitive, these findings are not exclusive to IIMs, yet they allow the identification of the best biopsy site to diagnose DM. Once the diagnosis is established, MRI is a useful tool to monitor disease activity, and check for residual inflammation and relapses. A high T1-weighted signal allows the identification of fatty substitution of muscle cells in atrophic muscles, quantifying disease damage.

Diagnostic and Classification Criteria

DM needs to be suspected according to specific clinical clues, which include proximal muscle weakness and typical skin rash as observed and assessed by an expert physician. By integrating laboratory and histological data a final diagnosis can be made. The presence of pathognomonic cutaneous manifestations facilitates the diagnosis, possibly sparing the patient from undergoing a muscle biopsy, though a skin biopsy is still highly recommended by the experts to show the characteristic interface dermatitis and exclude dermatologic mimickers, such as psoriasis, eczema, and multicentric reticulohistiocytosis [13]. Indeed, a meticulous diagnostic workup is always crucial in order to exclude mimicking conditions, such as muscular dystrophies, motor neuron diseases, dysmetabolic, and toxic myopathies, to name but a few. Therefore, the importance of collecting relevant anamnestic, clinical, and laboratory features cannot be undermined. A diagnosis of CADM can be made when cutaneous hallmark manifestations of classic DM are present for at

Table 31.3 Proposed minimal set of hallmark cutaneous manifestations of DM for the purpose of defining amyopathic DM for future clinical studies

Major cutaneous criteria:
- “Heliotrope rash”
- Gottron’s papules
- Gottron’s sign of DM

Minor cutaneous criteria
- Macular violaceous erythema (with or without associated scale/hyperkeratosis, pigmentary change, and/or telangiectasia) involving (involvement of each of the below anatomical regions qualifies as a single minor criterion):
  - Scalp and/or anterior hairline
  - Malar eminences of face and/or forehead and/or chin
  - V-area of neck and/or upper chest (open collar area; V-sign)
  - Nape of the neck and/or posterior aspects of shoulders (shawl sign)
  - Extensor surfaces of the arms and/or forearms
  - Linear streaking overlying extensor tendons of the dorsal aspects of the hands
  - Periungual areas
  - Lateral surface of thighs and/or hips
  - Medial malleoli
- Periungual nail fold telangiectasia and/or cuticular hemorrhage/infarct and/or dystrophic cuticles
- Poikiloderma (concurrence of hyperpigmentation, hypopigmentation, telangiectasia, and superficial atrophy)
- Mechanic’s hand lesions
- Cutaneous calcinosis
- Cutaneous ulcers
- Pruritus and/or cutaneous burning sensation

The hallmark cutaneous manifestations of DM will be presumed to be present if the following conditions are met: the presence of two major criteria or one major criterion and two minor criteria (biopsy of at least one skin lesion should show changes consistent with cutaneous DM)

These criteria were originally presented and discussed at the Third Annual Meeting of the Medical Dermatology Society in San Francisco on March 20th, 1997

least 6 months without clinical signs of muscle involvement. A minimal set of hallmark cutaneous criteria has been proposed to facilitate CADM diagnosis (Table 31.3) [1].

The discovery of MSA and the increasing availability of commercial kits for their identification is revolutionizing such paradigm further questioning the central role of muscle biopsy and allowing the identification of IIM patients presenting with organ involvement different from skin and skeletal muscle, such as patients with ILD bearing anti-MDA5 or anti-Jo1 antibodies. Once a diagnosis has been established, searching for associated CTD and exclusion of associated malignancies are crucial.

Over the years, the scientific community has tried to elaborate diagnostic and classification criteria to help clinicians in the identification of IIM patients and their inclusion in clinical studies.

The 1975 Bohan and Peter’s Diagnostic Criteria represent a milestone of such effort [14]. Bohan and Peter empirically elaborated a set of five criteria to identify and classify a patient as having “definite,” “probable,” and “possible” DM or PM. DM is defined as definite/probable/possible when 3/2/1 of the criteria are present together with the “skin criterion,” and alternative diagnoses have been excluded. DM could then be subcategorized into JDM, CAM, and CTD-associated DM. Even though Bohan and Peter’s Criteria represent a milestone in the field of IIMs, they were burdened by a series of limitations. The criteria were empirically derived on a limited cohort of patients from a single center, provide a poor definition of the items required for diagnosis and require a not better-defined exclusion of differential diagnosis. These criteria originally showed high sensitivity in discriminating PM from DM and high specificity in differentiating patients with IIM from patients with other CTDs (>93%) [15], but later studies comparing their performance in identifying IIMs from other myopathies and neuromuscular diseases showed much poorer results with specificities as low as 29% [15].

In 1997, Targoff et al. proposed an updated version of the Bohan and Peter’s Criteria which included the known MSA (anti-Mi2, anti-SRP, and ARS) as the sixth item, and muscle inflammation on MRI as an alternative to the elevation of muscle enzymes or muscle weakness criteria [16]. Such revised criteria were proposed as diagnostic criteria and later showed significant levels of specificity and sensitivity in identifying patients with IIMs (Table 31.5).

In 2003, Dalakas and Hohlfeld proposed a set of diagnostic criteria highly focused on muscle histology, which was central in distinguishing between PM and DM [6]. They also included amyopathic dermatomyositis as a diagnosis for those patients with typical DM skin rash without clinically overt muscle weakness and a specific/negative muscle biopsy. Great limitations to these criteria are represented by the exclusion of MSA and MRI in the diagnostic workup together with the inadequacies of a histology-centered method in distinguishing PM from Inclusion Body Myositis.

Table 31.4 EULAR/ACR classification criteria [13]

Variable	Score No muscle biopsy	 Muscle biopsy
Age of onset of first symptom assumed to be related to the disease ≥18 years and < 40 years	1.3	1.5
Age of onset of first symptoms assumed to be related to the disease ≥40 years	2.1	2.2
Muscle weakness		
Objective symmetrical weakness, usually progressive, of the proximal upper extremities	0.7	0.7
Objective symmetrical weakness, usually progressive, of the proximal lower extremities	0.8	0.5
Neck flexors are relatively weaker than neck extensors	1.9	1.6
In the legs, proximal muscles are relatively weaker than distal muscles	0.9	1.2
Skin manifestations		
Heliotrope rash	3.1	3.2
Gottron Papules	2.1	2.7
Gottron Sign	3.3	3.7
Other clinical manifestations		
Dysphagia or esophageal dysmotility	0.7	0.6
Laboratory measures		
Anti-histidyl-transfer RNA synthetase (Jo1) autoantibody present	3.9	3.8
Elevated serum levels of one of the following enzymes: Creatinine kinase, lactate dehydrogenase, aspartate aminotransferase, or alanine aminotransferase	1.3	1.4
Muscle biopsy features- the presence of		
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers		1.7
Perimysial and/or perivascular infiltration of mononuclear cells		1.2
Perifascicular atrophy		1.9
Rimmed vacuoles		3.1

Muscle biopsy available
- Probable IIMs: aggregated score ≥ 6.7 and < 8.7 (probability ≥55% and < 90%)
- Definite IIMs: aggregated score ≥ 8.7 (probability ≥90%)

Muscle biopsy not available
- Probable IIMs: aggregated score ≥ 5.5 and < 7.5 (probability ≥55% and < 90%)
- Definite IIMs: aggregated score ≥ 7.5 (probability ≥90%)

The need for new, updated, data-driven classification criteria led to the publication of the 2017 EULAR/ACR classification criteria (Table 31.4) [13]. Candidate variables were chosen via expert opinion and already existing criteria; 16 items were finally selected and given a weighted score (Table. 31.4). The sum of the scores of a patient reflects the probability of the same patient having IIMs and specific cutoffs were derived to define "possible," "probable," and "definite" IIM. Two sets of cutoffs were actually generated according to whether muscle biopsy is available or not (see Table. 31.4 for the specific cutoffs). A patient falling into the "probable" DM category can be classified as having DM as this category shows the best balance between specificity and sensitivity.

Once a diagnosis of IIM is made, a classification tree is used to subclassify the patients.

An online calculator was developed (http://www.imm.ki.se/biostatistics/calculators/iim).

The criteria were internally validated in a cohort of 976 IIM patients and 624 non-IIM patients with mimicking conditions, and their performances were compared with the existing criteria both for IIM identification and subclassification, showing the overall superiority of the EULAR/ACR criteria (Table 31.5). The EULAR/ACR criteria are data-driven, easy to use, and highly accessible, however they are not devoid of drawbacks. To be as accessible as possible, MRI was excluded as its use, although still recommended, is burdened by high costs and the need for not-always-available expertise. Among the MSA antibodies, only anti-Jo1 antibodies are included for the following reasons. First of all, only they were observed a significant number of times in the validation cohort, which was recruited between 2008 and 2011. At that time not all MSA were identified or routinely screened. Still today MSA identification methods are yet to be standardized and the available commercial kits are expensive limiting their use. Being classification criteria, the EULAR/ACR criteria were tested on patients having an established diagnosis from at least 6 months, therefore excluding patients with new-onset disease. Moreover, they fail to include items regarding manifestations other than myositis and skin disease, such as arthritis and ILD. Therefore, notwithstanding the great advances represented by the EULAR/ACR classification criteria, there is still a large margin for improvement, and the probability model used for their development offers good possibilities for future updates. In 2018, another set of classification criteria was proposed during the 236th European Neuromuscular Center (ENMC) International Workshop. Differently from the EULAR/ACR

Table 31.5 Performances of classification/diagnostic criteria according to 2017 EULAR/ACR classification criteria [13]

	EULAR/ACR[a]					
Performance	No biopsy	Biopsy	Bohan and Peter[b]	Targoff et al.[b]	Dalakas and Hohlfeld[b]	ENMC[b]
Sensitivity, mean (95%CI)	87 (84–90)	93 (89–95)	98 (96–99)	93 (90–95)	6 (5–8)	52 (48–55)
Specificity, mean (95%CI)	82 (77–87)	88 (83–93)	55 (50–61)	89 (84–92)	99 (98–100)	97 (95–98)
PPV, mean	90	94	95	95	92	96
NPV, mean	79	85	90	85	43	57
Correctly classified, mean	86	91	86	91	45	70
Correct classification of IIM per subgroup[c] (%)						
Amyopathic DM	94	60	25	0	0	0
DM	96	98	100	99	7	83
Hypomyopathic DM	83	100	80	67	0	20
IMNM	100	100	100	100	0	10
IBM	58	94	97	91	1	1
JDM	97	96	100	98	5	86
PM	79	86	95	85	11	9

ACR American College of Rheumatology, *DM* dermatomyositis, *ENMC* European League Against Rheumatism, *IBM* inclusion body myositis, *IMNM* immune-mediated necrotizing myopathy, *JDM* juvenile dermatomyositis, *NPV* negative predictive value, *PM* polymyositis; PPV: positive predictive value

[a] Cutoff probability:55%

[b] Definite and probable polymyositis and dermatomyositis

[c] Classification as idiopathic inflammatory myopathy per subgroup out of total number of cases per subgroup, expressed as mean

criteria, they allow classifying a patient as having DM in the presence of a typical DM skin manifestation plus any of the DM-specific antibodies, being anti-TIF1γ, anti-Mi2, anti-MDA5, anti-SAE, and anti-NXP2 [17].

Therapy

Glucocorticoids (GCs) represent the mainstay of therapy in the acute phase of the disease. Prednisone equivalent dose of 1 mg/kg/day is the standard initial dose in DM, although lower doses can be used in cutaneous-limited disease and pulses of GCs can be used in severe, life-threatening cases, such as patients presenting with rapidly progressive ILD (RP-ILD) or dysphagia/respiratory failure due to muscle weakness [1]. Immunosuppressants are added to the GCs regime both in the initial and in the maintenance phase. Methotrexate (7.5–20 mg/week), azathioprine (1.5–2.5 mg/kg/die), and mycophenolate mofetil (1000–2000 mg/die) are well-known drugs with a good profile of tolerability and efficacy on both muscle inflammation and skin disease. Calcineurin inhibitors, cyclosporine, and tacrolimus are usually second-line drugs. They can be used as stand-alone immunosuppressants or as add-on therapy and are compatible with pregnancy. Cyclophosphamide (1–2 mg/kg/die orally or 0.75–1 g/m^2 e.v. every month for 5–6 months) is reserved for refractory cases or highly aggressive forms of the disease, including RP-ILD. Rituximab has become increasingly important in the management of IIMs being particularly effective in muscle disease and ILD. Some MSAs can predict good response to rituximab, such as anti-Mi2 and ASS antibodies [4]. JAK inhibitors are a new class of synthetic-targeted disease modifying anti-rheumatic drugs (st-DMARDs), which have been proven effective in several autoimmune conditions. Their use in DM and IIMs has just started to be unveiled and clinical trials are ongoing. Real-life use of JAK-inhibitors in IIMs seems to point to a good efficacy of this class of drugs on calcinosis, which is usually treatment–resistant [18]. Hydroxychloroquine is also a valid alternative to control cutaneous manifestations of the disease.

Immunoglobulins (2 g/kg/month) have shown good efficacy in the management of severe myositis. Their use is usually reserved to patients with dysphagia, very severe muscle weakness/muscle damage, or fragile patients [19]. Plasmapheresis has also been used in very severe cases of DM, particularly in anti-MDA-associated RP-ILD.

Prognosis

Patients with IIMs have increased mortality with respect to the general population with a 10-year survival ranging from 20% to 90% [20]. A recent nationwide population-based study in Sweden showed a hazard ratio of 7.95 for DM mortality with respect to the general population. Such a trend was observed in all age groups and irrespective of sex [20]. Major causes of death were malignancies, cardiovascular disease, and respiratory disease [20]. Pneumonia and ILD represented major causes of hospitalization. MSA can help in stratifying patients according to risk of death as patients with anti-Mi2 antibodies, for instance, carry a more favorable prognosis, while patients with anti-MDA5 antibodies are at higher risk of morbidity and mortality in the short term.

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Sporadic Inclusion Body Myositis

32

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and Jose Milisenda

Abstract

Sporadic inclusion body myositis (sIBM) is currently considered one of the five main phenotypes of the inflammatory myopathies, besides polymyositis, dermatomyositis, immune-mediated necrotizing myopathy, and the antisynthetase syndrome. It is the most common acquired muscle disease in elderly individuals, particularly men. Its prevalence varies among ethnic groups but is estimated to range between 1 to 182 per million among those aged 50 and older, this wide range depending on the variability of the diagnostic criteria used. Genetic as well as environmental factors and autoimmune processes might both have a role in its pathogenesis. Unlike other inflammatory myopathies, sIBM is a slowly progressive disease, having a distinctive pattern of muscle involvement and different forms of clinical presentation. In some cases, a primary autoimmune disease coexists. Diagnosis is suspected on clinical grounds and is established by typical muscle pathology. However, current criteria allow for a diagnosis on clinical grounds in absence of some characteristic pathological features. As a rule, sIBM is refractory to conventional forms of immunotherapy.

Keywords

Sporadic inclusion body myositis · D\iagnostic criteria · Classification · Inflammatory myopathy · Autoimmunity

Description of the Disease

Sporadic inclusion body myositis (sIBM) is an acquired progressive muscle disease characterized by a specific clinical phenotype and CD8-lymphocyte MHC-I restricted inflammatory endomysial infiltrate together with characteristic rimmed vacuoles in muscle biopsy [1, 2]. Largely considered one of the main five phenotypes of the group of myositis, being polymyositis, dermatomyositis, immune-mediated necrotizing myopathy, and the antisynthetase syndrome the other four [3], sIBM presents with some clearly differentiated features, such as the refractory response to immunosuppressive treatment, and that may be particularly associated with Sjögren syndrome [4] and to hematologic malignancies, especially T cell large granular lymphocytic leukaemia [4, 5]. The association with C virus hepatitis infection seems to be irrelevant. No other types of associations with solid malignancies have been until now reported.

sIBM is probably the most common acquired myopathy in patients above 50 years, affecting men more frequently. Its prevalence varies notoriously among ethnic groups but is estimated to range between 1 to 182 per million among those aged 50 and older, this wide range depending on the variability of the diagnostic criteria used. A population-based

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study performed in Norway, with sIBM classified by ENMC 2011 sIBM criteria disclosed a higher prevalence of 3.3 per 100,000 inhabitants [6].

Clinical phenotype may be so characteristic, that even in absence of muscle biopsy clinicians may achieve the correct diagnosis. Current diagnostic criteria [7, 8] (see below) includes the option of a diagnosis of sIBM based only on clinical grounds. Distal and proximal weakness, asymmetry of muscle involvement, frequent presence of dysphagia, and occasional facial weakness in a male older than 50 years, formerly diagnosed with "treatment refractory polymyositis" may account for a typical vignette of sIBM.

sIBM has predilection for finger flexors and knee extensors (quadriceps) often asymmetric. Patients may present with difficulty with stairs or rising from a low seat. Handgrip weakness or difficulty with the shoelaces may also be present. Foot drop due to mild weakness of ankle dorsiflexion is also a characteristic finding in advanced cases. Asymmetric quadriceps wasting (Fig. 32.1) and difficulty to make a fist can be easily detected at physical examination by the astute and experienced clinician, suggesting the diagnosis of sIBM.

Partial invasion of non-necrotic muscle cells by an endomysial infiltrate (CD8$^+$ T cell predominant), rimmed vacuoles probably because of autophagic degeneration of the muscle fibers, and universal upregulation of sarcolemmal MHC I are considered canonical pathological features of sIBM although not all the patients present the full constellation of these findings (Fig. 32.2). Protein aggregates including β-amyloid, TDP-43 or p62 protein [9, 10], and mitochondrial abnormalities such as ragged-red fibers as well as cytochrome oxidase (COX)-negative fibers may also support the diagnosis. Presence of 15–18 nm filamentous inclusions may be seen on electron microscopy (Fig. 32.3).

Etiopathogenesis of the disease is largely unknown although autoimmune-associated diseases (Sjögren syndrome) and hematological malignancies (large granular lymphocytes leukemia) may play a relevant role in some cases. Genetic [11], environmental (aging), inflammation, and misfolded protein accumulation undoubtedly impact in its pathogenesis. Mitochondrial dysfunction seems to play

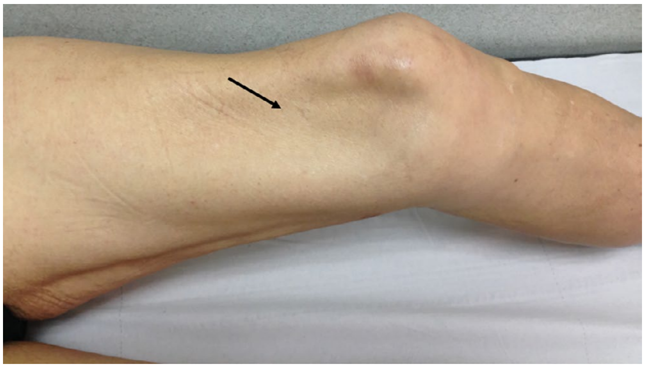

Fig. 32.1 Quadriceps atrophy (arrow) in an elderly man diagnosed with sporadic inclusion body myositis

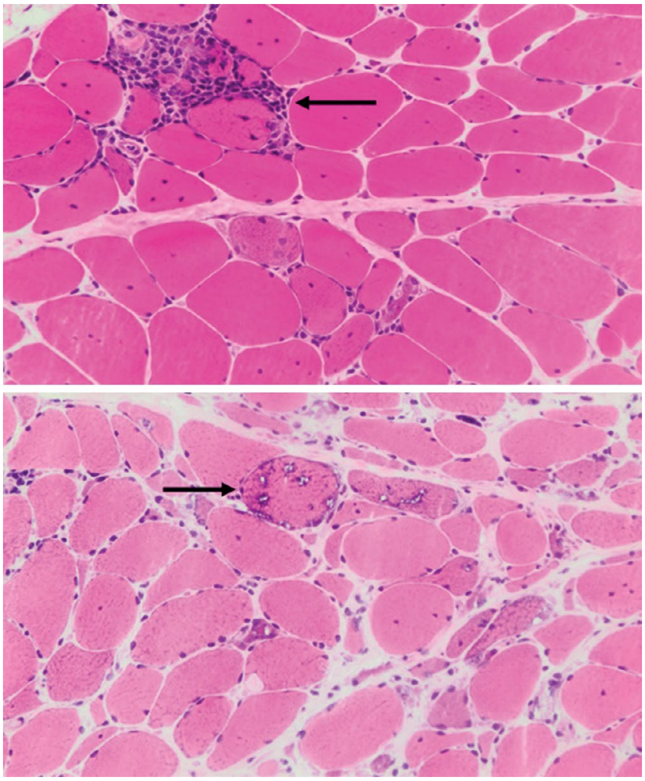

Fig. 32.2 Muscle biopsy from a patient diagnosed with sIBM. Upper picture: cross-sectional H&E stained muscle-biopsy sample with endomysial inflammatory infiltrate invading non-necrotic cells (arrows). Lower picture: Cross-sectional H&E stained muscle-biopsy sample with numerous rimmed vacuoles (arrows)

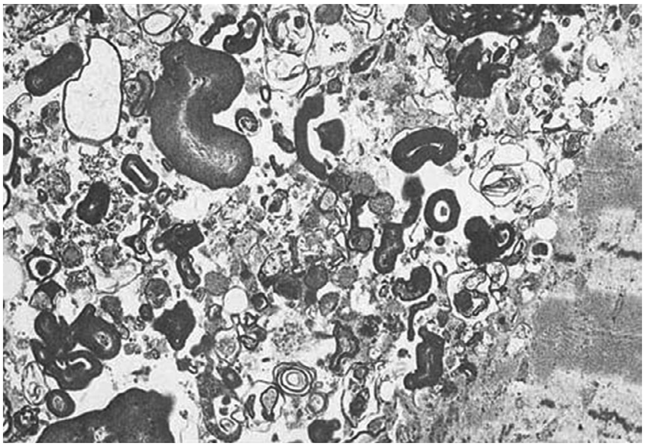

Fig. 32.3 Cytoplasmic filamentous inclusions in a case of sporadic inclusion body myositis (sIBM). Electron microscopy

a not yet well-defined role in the pathogenesis of the disease [12].

Main signs and symptoms of sIBM and laboratory findings and serological markers are shown in Tables 32.1 and 32.2. Table 32.3 contains the main disease to be considered in the differential diagnosis of patients with sIBM.

Table 32.1 Signs and symptoms of sIBM

Weakness of deep finger flexors (90%)
Knee extension weakness due to quadriceps involvement (90%)
Dropped head and camptocormia (axial weakness) (15%)
Limb weakness (50%)
Dysphagia (60%) (aspiration pneumonia its main complication and cause of death)
Wheelchair dependent due to muscle weakness progression (90% at 20 years from onset)

Table 32.2 Laboratory findings and serological markers

Positivity to anti-anticytosolic 5′-nucleotidase 1A (anti-cN1A)[a]
Occasional positivity to any of the myositis-specific and associated autoantibodies
sCK no greater than 15 × ULN

[a] Detected in 50% of patients but may be positive also in other systemic diseases such as Sjögren syndrome or systemic lupus erythematosus [13, 14]

Table 32.3 Differential diagnosis for sIBM (from ref. [1])

Motor neuron disease	Hyperreflexia, cramps, fasciculations, typical EMG
Polymyositis	Subacute (weeks to months), proximal and symmetrical muscle weakness, high CK levels
Vacuolar myopathies: (myofibrillar myopathies, non-sporadic IBM)	Lack of inflammation, negative MHC HLA-class I

Diagnostic Criteria

There has been some controversies with the diagnostic criteria in sIBM. From the very onset in the 1990s, patients with sIBM were recognized in those diagnosed with the Bohan and Peter criteria for polymyositis who do not respond to conventional immunosuppressive therapy. The proposed criteria by Griggs et al. [15] were set up in 1995 and initially focused on pathological features independent of the clinical features, establishing that for a definite sIBM diagnosis it was mandatory to detect in the muscle biopsy all three pathological findings: inflammatory infiltrate with partial invasion, rimmed vacuoles, and either amyloid deposits or 15- to 18-nm tubulofilaments. However, different groups reported cases of sIBM without characteristic muscle pathology, and other with rimmed vacuoles and an alternative diagnosis different to sIBM.

In 2011, a workshop held by the ENMC established the current diagnostic criteria that allow the diagnosis of sIBM in absence of typically pathological findings (clinically defined sIBM) besides the clinic-pathological defined sIBM (see Table 32.4) [8]. This allows to include more patients to clinical trials to determine which therapeutic strategies will be worth for these patients. As a rule, all the published (until now) criteria for sIBM have a high specificity (98–100%) and sensitivity using the ENMC (2011) criteria, was 88% for the "probable sIBM," 57% for the "clinically defined sIBM," and 15% for the "clinico-pathologically defined sIBM" [16].

Criticism of Diagnostic Criteria

Other interesting tools may be used or added to improve mainly the sensitivity of the proposed criteria. Antibodies against cytosolic 5′-nucleotidase 1A (cN1A) although may

Table 32.4 The ENMC IBM research diagnostic criteria 2011

Clinical and laboratory features	Classification	Pathological features
Duration >12 months Age at onset >45 years Knee extension weakness ≥ hip flexion Weakness and/or finger flexion weakness > shoulder abduction weakness sCK no greater than 15 × ULN	Clinico-pathological defined IBM	All of the following: Endomysial inflammatory infiltrate Rimmed vacuoles Protein accumulation[a] or 15- to 18-nm filaments
Duration >12 months Age at onset >45 years Knee extension weakness ≥ hip flexion Weakness and finger flexion weakness > shoulder abduction weakness sCK no greater than 15 × ULN	Clinically defined IBM	One or more, but not all, of: Endomysial inflammatory infiltrate Upregulation of MHC class I Rimmed vacuoles Protein accumulation[a] or 15- to 18-nm filaments
Duration >12 months Age at onset >45 years Knee extension weakness ≥ hip flexion Weakness or finger flexion Weakness > shoulder abduction weakness sCK no greater than 15 × ULN	Probable IBM	One or more, but not all, of: Endomysial inflammatory infiltrate Upregulation of MHC class I Rimmed vacuoles Protein accumulation[a] or 15- to 18-nm filaments

[a] Demonstration of amyloid or other protein accumulation by established methods (e.g., for amyloid Congo red, crystal violet, thioflavin T/S, for other proteins p62, SMI-31, TDP-43). Current evidence favors p62 in terms of sensitivity and specificity, but the literature is limited, and further work required (ref. [8])

be also positive in patients with other autoimmune diseases [17], appear in nearly a 50% of patients with sIBM, and seem to be related with a worse prognosis, its incorporation to the current diagnosis criteria may help to define more severe cases. Muscle MRI as a diagnostic tool in sIBM is limited; however, prominent fatty muscle infiltration (oedema on T2 signal) and asymmetric involvement of quadriceps and medial gastrocnemius muscle should rise suspicion of sIBM. β-amyloid detection within the muscle by means of amyloid positron emission tomography (amyloid-PET) using [18F] florbetapir may be useful for sIBM diagnostic mainly to differentiate from true polymyositis [18]. Moreover, a recent published study reported that a novel investigational PET tracer may allow to visualize in vivo whole-body skeletal muscle CD8 T cells, which will be of paramount relevance as a biomarker of the disease [19].

If these new advances accounting for the immunological profile or functional image will be of interest and useful for a sIBM, diagnostic improvement need to be analyzed in future studies. Recently, a ENMC workshop [20] that probably may address these, and other relevant issues focused on the disease has been held although the full report has not yet published.

Short Paragraph on Therapy and Prevention

No effective drug treatments are available for sIBM, and it is considered a refractory disease to conventional immunosuppressive therapy [1, 2]. Other strategies targeting muscle atrophy pathways, such as monoclonal antibodies against myostatin, a physiologic inhibitor of the skeletal muscle mass, have failed [21]. Nevertheless, manifestations such as dysphagia, respiratory failure, or muscle mobility must be addressed by the treating physicians.

Dysphagia screening is recommended on an annual basis due to relevance of associated aspiration pneumonia as the main cause of death in these patients. Cricopharyngeal bar due to scaring of cricopharyngeal muscle may be addressed in specific cases by cricopharyngeal myotomy, endoscopic dilatation, or botulinum toxin injection. Intravenous immunoglobulin may be useful in some cases with severe dysphagia, and it is worth to use it. Respiratory failure due to ventilatory insufficiency due to muscle weakness may occur at advanced stages. Pulmonary function test and nocturnal oximetry may assist the clinicians to take the proper decisions. Rehabilitation periodic evaluation is endorsed to know if the patients may benefit from assisted devices such as walkers or wheelchairs to maintain mobility. There is no place for general prevention strategies in patients with sIBM given the scarce knowledge about the etiopathogenesis of the disease.FundingInstituto de Salud Carlos III co-financed by the European Regional Development Fund (ERDF) PI18/01609.

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Antisynthetase Syndrome

33

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Abstract

Antisynthetase syndrome (ASS) is classified as a subset of idiopathic inflammatory myopathies (IIM). Its clinical manifestations encompass more than muscular involvement, including interstitial lung disease (ILD), arthritis, fever, characteristic cutaneous lesions, and Raynaud's phenomenon. Additionally, a distinctive muscle biopsy pattern is often observed. The diagnosis is based on the detection of myositis-specific antibodies targeting aminoacyl tRNA synthetase, supported by relevant clinical, pathological, and radiological findings. To date, eight antisynthetase antibodies (ASA) have been identified, with antibodies against histidyl-tRNA synthetase (anti-Jo-1) being the most prevalent. While explicit diagnostic or classification criteria for ASS remain unestablished, the presence of a primary clinical feature coupled with the corresponding autoantibody is generally indicative of the syndrome.

Keywords

Antisynthetase syndrome · Myositis · Arthritis · Interstitial lung disease · Antisynthetase antibodies · Raynaud's phenomenon

Introduction

Antisynthetase syndrome (ASS) is an autoimmune disease characterized by the presence of aminoacyl tRNA synthetase autoantibodies (AuAb) or antisynthetase AuAb (ASA), which are a specific type of myopathy-associated antibody (MSA). These antibodies target cytoplasmic synthetases that facilitate ATP-dependent binding of single amino acids to their respective tRNA, ensuring accurate protein synthesis. Although 20 amino acids can be distinguished, antibodies have been found against only eight. Approximately 30% of IIM cases have ASA present, with anti-Jo-1 being the most common AuAb [1–3].

Accurately diagnosing IIM requires careful evaluation of both clinical and radiological features in addition to expertise in interpreting serological tests. This is best accomplished in a collaborative environment, where clinical and diagnostic teams exchange information to ensure precise diagnosis and treatment decisions.

Epidemiology

Although the first cases of anti-synthetase syndrome (ASS) were described over 30 years ago, reliable epidemiological data is still lacking. ASA has been detected in 11.1–39.19% of patients with idiopathic inflammatory myopathies (IIM), and the worldwide prevalence of ASS is estimated to be 1–9 per 100,000 population. Nonetheless, exact figures on disease incidence remain unavailable. A study conducted in Manchester showed that IIM had a mean incidence of 17.6 cases per 1,000,000 person-years, as per the classification criteria of the European League Against Rheumatism

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(EULAR)/American College of Rheumatology (ACR). After expert consensus, 28% of the cases were identified as ASS [4].

Females experienced the disease more often than males, and the mean age of onset ranged from 43 to 60 years [1–3].

Clinical Manifestations

ASS is characterized by a combination of symptoms and signs, including myositis, arthritis, ILD, Raynaud's phenomenon, mechanic's hands (Fig. 33.1), and fever. The prevalence of each manifestation varies depending on the reported cohort and the ASA subtype. Generally, ASS patients most commonly experience muscular involvement and ILD, with the other symptoms being less prevalent (Table 33.1). It should be noted that manifestations may emerge gradually over time, depending on the ASS subtype. For instance, at disease onset, patients with anti-Jo-1 AuAb typically present with isolated arthritis, while individuals who are positive for anti-PL-7 or anti-PL-12 commonly manifest isolated ILD. After months to years of follow-up, most patients display the classical triad of myositis, arthritis, and ILD. However, isolated ILD still remains the most frequent manifestation in individuals with anti-PL-12, and isolated myositis in those who are anti-OJ positive.

Myositis

The spectrum of muscular involvement in ASS varies from increased serum concentrations of muscle enzymes to severe weakness and mobility impairments. Typically, patients experience weakness in the proximal muscles of their upper and lower extremities. Additionally, one-third of patients exhibit neck muscle weakness and involvement of the esophageal muscles, resulting in dysphagia. Anti-Jo-1-positive patients, in particular, have a higher likelihood of experiencing muscle weakness compared to anti-PL-7 or anti-PL-12-positive patients. On the flip side, patients who have anti-OJ AuAb are vulnerable to developing more severe myositis (Table 33.1). Almost 65% of patients with ASS displayed anomalies during MRI scans of their thigh muscles. Muscle inflammation is predominantly noticed in the front section, while damage and fatty replacement mostly affect the back section.

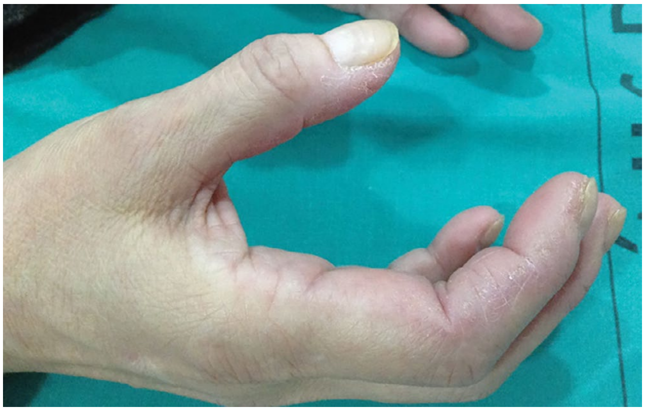


Fig. 33.1 Fissuring and cracking of the palms and fingers compatible with mechanic's hands

Interstitial Lung Disease

Interstitial lung disease (ILD) is found in 50.67–100% of patients with ASS, depending on the ASA subtype (Table 33.1). ILD is frequently the first manifestation in patients with anti-PL-7, anti-PL-12, and anti-EJ antibodies. ILD is more prevalent among anti-PL-7 and anti-PL-12-positive patients compared to other ASA subtypes throughout the course of ASS. Additionally, patients with anti-PL-7 and anti-PL-12 antibodies experience, more frequently, symptomatic, persistent, and severe ILD. However, approximately 20% of patients experience an asymptomatic course of ILD, which occurs more often in cases of anti-Jo-1 than in people with other ASA types [5, 6].

According to Fig. 33.2, HRCT imaging indicates that 78–100% of ASS-ILD patients display a nonspecific interstitial pneumonia (NSIP) or organizing pneumonia (OP) pattern. Fibrosis and honeycombing are infrequent during the early stages of the disease, but as ILD persists, they tend to become more widespread. Additionally, some patients display the typical interstitial pneumonia (UIP) pattern. Patients harboring anti-PL-7 and anti-PL-12 antibodies display more pronounced fibrosis in their ILD than those who are anti-Jo-1 positive. Precapillary Pulmonary Hypertension (PH) is reported to occur in 7.9% of ASS patients, usually resulting from ILD [7].

Arthritis

Arthritis is a prevalent condition, with a prevalence ranging from 20% to 88%, especially in anti-Jo-1 patients. It can be the first and most common manifestation and usually affects the proximal interphalangeal, metacarpophalangeal, and wrist joints in a symmetrical pattern. The larger joints like the knees, elbows, shoulders, ankles, hips, as well as the distal interphalangeal or feet joints, are less commonly involved. It has been observed that an erosive form is associated with calcinosis of the distal fingers.

The prevalence of anti-cyclic citrullinated peptide antibodies (ACPA) in ASS patients with arthritis ranges from 4.96% to 13.5%, whereas rheumatoid factor is present in as many as 31.5% of patients [8].

Table 33.1 Antisynthetase antibodies and relation to main clinical manifestations

Name	Antigen	Test	Frequency (%)	ILD (%)	Myositis (%)	Arthritis (%)	Other clinical features
Jo-1	Histidyl-tRNA synthetase	ID; IP; WB; EIA	22–73	69–80	84–95	74%	Arth (60); RP (60); MH(70); Fever
PL-7	Threonyl-tRNA synthetase	ID; IP; EIA	10–18	75 (severe)	66	50%	Heliotrope rash, pericardial effusions
PL-12	Alanyl-tRNA synthetase	ID; IP; EIA	6–17	91 (severe, sometimes isolated)	33	42%	RP
OJ	Isoleucyl-tRNA synthetase	IP; WB; EIA	2–5	44–61%	44 (could be severe)	44%	Lower incidence RP
EJ	Glycyl-tRNA synthetase	IP; WB	2–23	98	56	53%	
KS	Asparaginyl-tRNA synthetase	IP	3–8	100 (usually isolated)	5	–	
ZO	Phenylalanyl-tRNA synthetase	IP	Rare	–	–	–	
HA/YRS	Tyrosyl- tRNA synthetase	IP	Rare	–	–	–	

EIA enzyme-immunoassay, *ILD* interstitial lung disease, *IP* immunoprecipitation, *MH* mechanic hands, *RP* Raynaud's phenomenon, *WB* Western blot

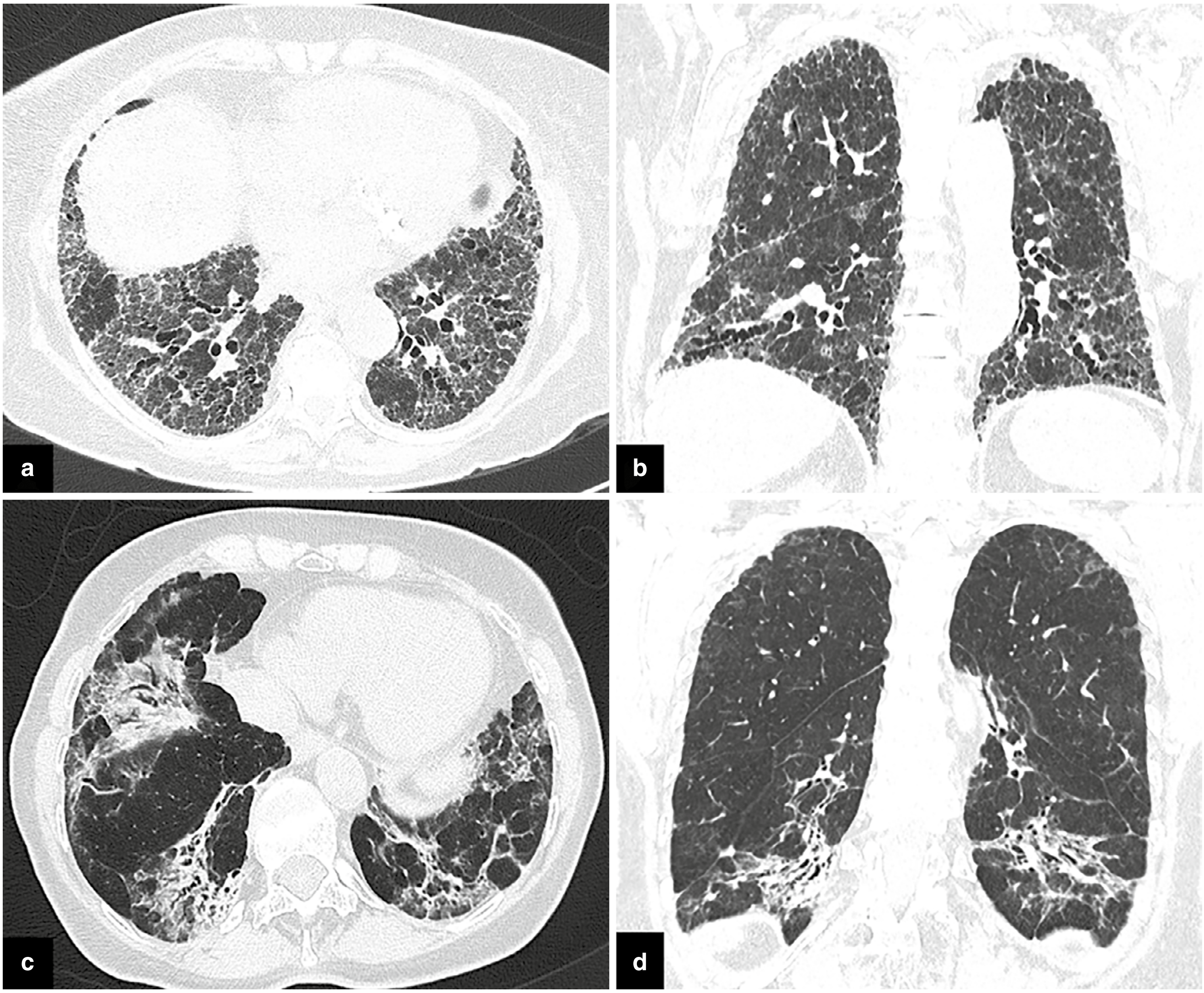


Fig. 33.2 HRCT patterns in two patients with ASS. Fibrotic NSIP pattern: axial (**a**) and coronal (**b**) reconstructions show diffuse ground glass and reticular opacities with central traction bronchiectasis. Organizing pneumonia pattern (**c**, **d**) basal predominant peribronchovascular consolidations and perilobular distribution

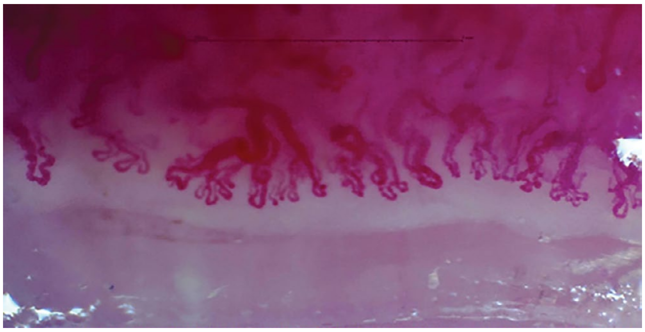


Fig. 33.3 Nailfold capillaroscopy: the capillary architecture is altered with a decrease in capillary density and the presence of complex and dilated ramifications. Image obtained using capillary.io software

Others

Mechanic's hands, characterized by scaly, fissured, and non-itching hyperkeratosis present on the palmar and lateral sides of the hands and fingers, represent a key feature of antisynthetase syndrome (ASS) (Fig. 33.1). This manifestation happens in roughly 35% of patients and is more frequently observed in individuals with anti-Jo-1 AuAb compared to other subtypes of ASA. Raynaud phenomenon is present in 38–50% of patients and is more commonly reported in subjects with polyarthritis than those with myositis and/or ILD. Fever, a nonspecific symptom, can nevertheless be very prevalent at the onset of the disease (25–60%). Concerning nailfold videocapillaroscopy, specific patterns have not been precisely defined; however, recognized abnormalities prevalent in patients with inflammatory myopathies may also be common in this group of patients (around 62.1%) and represent an ongoing area of research (Fig. 33.3).

Pathogenesis

ASS has a multifaceted etiology, frequently instigated by environmental factors such as airborne contaminants [2]. These triggers activate the immune system, involving T cells, B cells, NK cells, and dendritic cells. The breakdown of immune tolerance, influenced by genetic factors, estrogens, and microbiome alterations, results in self-reactivity. In ASS, the cleavage of self-proteins may instigate autoimmunity, with aminoacyl-tRNA-synthetases (ARSs) playing a pivotal function. Genetic predispositions, particularly HLA-II alleles [9], strongly correlate with inflammatory myopathies, such as ASS [10]. The adaptive immunity includes B cells, CD4+ and CD8+ T cells, cytokines like IFN-alpha, and anti-ARS autoantibodies, which contribute to the pathogenesis. The complexity of understanding ASS is amplified by the heterogeneity of the disease, the absence of specific biomarkers, and the wide range of clinical presentations, severity, and progression among patients [11]. The correlation between antibody titers and the disease's spectrum or prognosis remains unclear.

Histology

ASS displays diverse myopathological patterns, such as necrotizing myopathy, perifascicular necrosis, and atrophy (Fig. 33.4) [12]. Muscle biopsies disclose notable HLA-DR expression and tubuloreticular inclusions (TRIs), in conjunction with changes in connective tissue that include heightened alkaline phosphatase (ALP) activity and fibrosis [13].

The variations in pathological presentations among different ASS autoantibodies subtypes are notable. Anti-PL-7 ASS is linked to an increased incidence of necrotizing myopathy without perifascicular necrosis and a decreased vascular domain among adults. Patients with anti-OJ exhibit more instances of muscle fiber, necrotic fiber, regenerating fiber, and perifascicular atrophy scores, along with frequent elevations in perimysial ALP activity. Anti-EJ ASS is distinguished by a greater prevalence of perifascicular atrophy and more frequent endomysial fibrosis. Anti-Jo-1 ASS is characterized by reduced scores in domains like muscle fiber, necrotic fiber, regenerating fiber, and perifascicular atrophy. The subtype is also associated with specific perifascicular HLA-DR expression, more frequent HLA-ABC expression, perifascicular enhancement, and lower incidence of perimysial ALP activity and endomysial fibrosis. Anti-PL-12 ASS, on the other hand, is associated with lower inflammatory scores [13].

The diversity in the pathological and immunological features among ASS subtypes highlights the complex nature of this disease. Understanding these distinctions is critical for

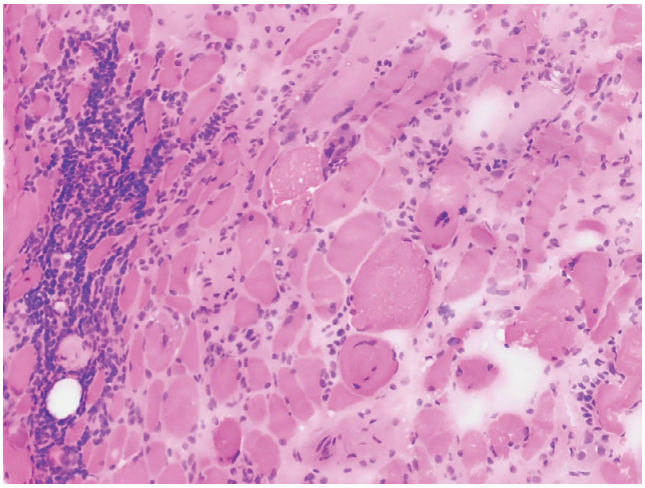


Fig. 33.4 Perivascular and perimysial (severe) and endomysial (moderate) inflammatory cells with perifascicular atrophy in a patient with anti-Jo1 AAS

subtype-specific diagnosis and treatment, as it grants an understanding of ASS mechanisms and highlights the importance of individualized management while acknowledging each subtype's unique characteristics [14].

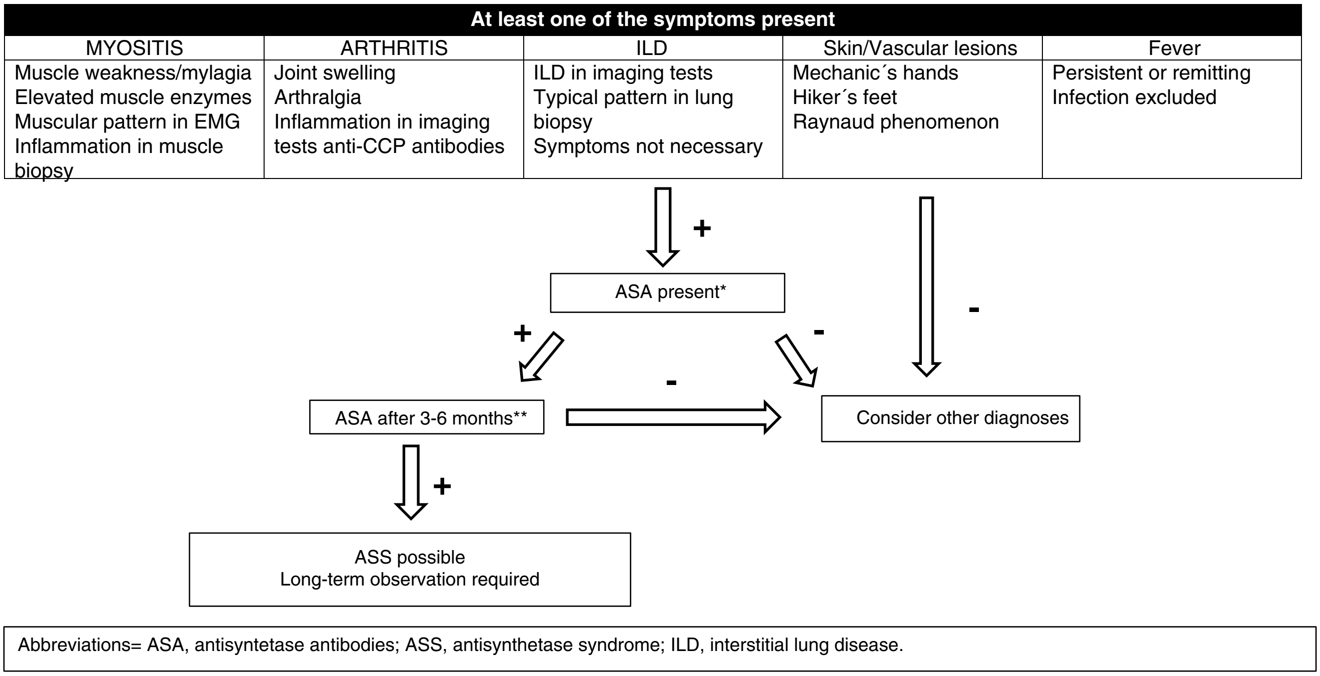
Serological Features

Aminoacyl-tRNA synthetases (ARSs) play a vital role in amino acid transfer for proper protein synthesis. The discovery of ASA has advanced our understanding of ASS, identifying 8 out of 11 known ARS antibodies in this context. Anti-Jo-1 autoantibodies, targeting histidyl-tRNA synthetase, were first described in 1980 and correlate strongly with inflammatory myopathy, particularly polymyositis. Various AuAbs, including anti-PL7, -PL12, -EJ, -OJ, -KS, -Zo, and -Ha/YRS, were later identified in patients with myositis. ASA is widely believed to be mutually exclusive, and most ASS patients do not possess other MSA such as anti-Mi-2, anti-PM-Scl, or anti-SRP. Each ASA is associated with ILD, either alone or with myositis [15]. Anti-Ro52 AuAb is prevalent among ASA-positive patients (30–65%), with a suggested correlation to ILD severity. Harmonizing testing methods for anti-synthetase syndrome (ASA) is essential, with immunoprecipitation remaining the reference method, despite line/dot-blot and ELISA being more commonly used in clinical practice. Sensitivity and specificity limitations persist in commercial assays for ASA detection. Though indirect immunofluorescence assay (IFA) may result in most antismooth muscle antibodies revealing cytoplasmic staining of HEp-2 cells, this approach is not particularly sensitive. Nevertheless, a cytoplasmic staining pattern identified on IFA enhances the positive predictive value of other methods. If multiple MSA are detected, or if clinical features are inconsistent with initial positive or negative ASA results, it may be necessary to confirm the findings with a different method [16].

Diagnostic Criteria

ASS currently lacks a formalized definition and classification criteria. However, in the last 10 years, there have been notable advancements in the classification and diagnostic parameters of IIM and their respective subtypes. Prominent among these advancements are Solomon's [5] and Connor's criteria [17] for ASS, alongside the EULAR/ACR 2017 criteria for adult and juvenile IIMs [18], encompassing major subgroups. Nonetheless, a key limitation of the latter framework is its failure to include the distinctiveness of ASS, particularly in its omission of autoantibodies beyond anti-Jo-1 [19]. Insightfully, Greco et al. elucidate that the EULAR/ACR criteria were satisfied by 59.5% of patients under clinical suspicion of ASS, an inclusive percentage involving all anti-Jo1-positive cases, but only a mere 20% of patients expressing other autoantibodies. As a corrective measure, the authors propose a revision of the EULAR/ACR criteria, advocating for the assignment of equivalent weight to all ASA in congruence with the significance attributed to anti-Jo-1, a modification that would potentially embrace 95% of clinically diagnosed cases [20].

Collaborative groups like American and European Network of Antisynthetase Syndrome (AENEAS), alongside organizations such as the International Myositis Assessment and Clinical Studies Group and the European Reference Network for Rare Diseases, are leading pioneering efforts to comprehensively study ASS, unravel its intricate clinical and pathophysiological aspects, and establish a robust classification framework. Despite these endeavors, the ongoing nature of this initiative underscores the existing deficiency in firmly established criteria, posing challenges in precise patient classification. This challenge is amplified by the inherently nonspecific nature of some ASS clinical manifestations such as arthritis, myositis, and/or ILD. In this regard, instances where a patient presents with myositis, ILD, arthritis and mechanic's hands, without the presence of an ASA, classification as a patient with ASS may not be warranted, although a very high clinical suspicion exists. However, it is crucial to recognize that, in certain cases, this absence could almost certainly be attributed to the existence of a hitherto unrecognized antibody or to the inherent limitations posed by prevailing antibody testing methodologies. Conversely, in an opposite clinical scenario, patients presenting with ASA and ILD, but no other typical symptoms, such as myositis, could be classified under the rubric of interstitial pneumonia with autoimmune features (IPAF). In this sense, a comprehensive evaluation of the AENEAS cohort reported that 381 patients (47%) had no muscle involvement at disease onset, and 186 (23%) were without muscle involvement [19]. In many cases, the diagnosis of ASS can be elucidated by the coexistence of arthritis, commonly of the oligoarticular/asymmetric subtype rather than polyarticular/symmetric, in conjunction with concurrent or subsequent-onset ILD. The median onset of interstitial lung disease is reported as 14 months (with an interquartile range of 7.5–53 months). To increase the complexity of diagnosis, sometimes the therapy targeting one manifestation may delay the onset of another, thus masking underlying features. Due to numerous diagnostic challenges, final diagnosis is often delayed. An average diagnostic delay of 6 months has been reported for patients with anti-Jo-1 antibodies [19] and much longer in the case of anti-PL-7 and anti-PL-12-positive patients [15]. Consequently, a conclusive classification is the ASS requires the manifestation of at least one recognized indicator associated with the pertinent antibody, as expounded in Table 33.1. Opinc AH et al [2], in line with this approach, have proposed a diagnostic algorithm according to these two requirements (Fig. 33.5).



At least one of the symptoms present				
MYOSITIS	ARTHRITIS	ILD	Skin/Vascular lesions	Fever
Muscle weakness/mylagia Elevated muscle enzymes Muscular pattern in EMG Inflammation in muscle biopsy	Joint swelling Arthralgia Inflammation in imaging tests anti-CCP antibodies	ILD in imaging tests Typical pattern in lung biopsy Symptoms not necessary	Mechanic´s hands Hiker´s feet Raynaud phenomenon	Persistent or remitting Infection excluded

Abbreviations= ASA, antisyntetase antibodies; ASS, antisynthetase syndrome; ILD, interstitial lung disease.

* If high level of antibody title using a specific technique in a plausible clinical context, directly assume the diagnosis.
**Repeat antibody in case of low antibody title or low clinical suspicion.

Fig. 33.5 Proposed algorithm for patients with the ASS spectrum symptoms. Adapted by Opinc et al. [2]. *If high level of antibody title using a specific technique in a plausible clinical context, directly assume the diagnosis. **Repeat antibody in case of low antibody title or low clinical suspicion

Conversely, concerning the histological domain, the requirement for muscle biopsy in all ASA-positive patients with suggestive clinical IIM features is a topic of debate. Factors such as anamnesis, enzyme levels, EMG, and imaging contribute to this discourse. Simultaneous ASS clinical features may reinforce the diagnosis, even if Bohan and Peter's PM/DM criteria are not fully met. Therefore, while not mandatory, a biopsy is advisable in compatible clinical scenarios (with the antibody and typical manifestations) to confirm the diagnosis and reasonably exclude alternative conditions like inclusion body myositis (IBM) or immune-mediated necrotizing myopathies (IMNM).

Therapy

Treating ASS can be complex due to the lack of FDA-approved medications and limited comparative studies. Retrospective or uncontrolled data make it even more challenging. Thus, a comprehensive, individualized approach is necessary, and assessment should be based on clinical phenotype, severity, predominant involvement, autoantibodies, age, and comorbidities to tailor the best treatment plan [2, 14]. Corticosteroids are vital initial therapy for ASS treatment, with doses varying depending on the severity of the condition. Intermediate-high doses of prednisone or an IV bolus of methylprednisolone are recommended for acute or severe cases, while lower initial dosages are considered for milder courses.

Starting a steroid-sparing agent with prednisone at diagnosis has shown to improve survival rates and reduce relapses. Retrospective studies have shown that mycophenolate, azathioprine, and tacrolimus effectively stabilize pulmonary function tests, improve overall symptoms, and reduce corticosteroid usage, with no significant differences among them. Mycophenolate is frequently selected as a first-line treatment, while azathioprine is a viable alternative, particularly for active arthritis. Calcineurin inhibitors, such as tacrolimus (preferred) and cyclosporine, are utilized as first-line treatment or in refractory cases, with careful monitoring for hypertension and nephrotoxicity [2, 14, 20]. Methotrexate may be used as a steroid-sparing agent, especially for patients with significant arthritis or myositis. Its role in managing ASS-associated interstitial lung disease, however, warrants further study. Regular monitoring for potential side effects like hepatotoxicity is crucial.

For patients who are refractory or intolerant to first-line steroid-sparing agents, rituximab may be considered, particularly if there is concomitant ILD or a positive anti-Ro52. For patients with ASS and ILD whose condition continues to progress despite initial treatment, it is advisable to either add or switch their therapy [12, 17]. Nintedanib should be taken into consideration as an add-on therapy for those with progressive fibrosing-ILD. Cyclophosphamide may be a suitable option for those with rapidly progressive ILD but this is a rare occurrence. For severe and refractory muscular involvement cases, intravenous immunoglobulin (IVIG) may be a valid consideration. Other effective treatment options for ASS have been identified in several case studies, including JAK inhibitors (tofacitinib), and CD19-targeted CAR-T therapies. If necessary, individuals with severe or progressive symptoms may receive an evaluation for a lung transplant. It is crucial to incorporate non-pharmacological interventions like pulmonary rehabilitation and infection prevention strategies into the management plan. Overall, a tailored, multifaceted approach to address various therapeutic options and individual patient characteristics is necessary to manage ASS.

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34

Immune-Mediated Necrotizing Myopathy

Wafa Elgeadi Saleh and Sergio Prieto-González

Abstract

Immune-mediated necrotizing myopathy (IMNM) is the youngest subgroup within the idiopathic inflammatory myopathies, described by the European Neuromuscular Centre in 2004. Patients with IMNM clinically present significant proximal muscle weakness, along with markedly elevated creatine kinase levels, while extra-muscular manifestations are rare. Moreover, this disorder is characterized by the presence of fiber necrosis and minimal inflammatory infiltrate in the muscle biopsy. Three distinct subtypes of IMNM have been recognized: associated with anti-SRP antibody, associated with anti-HMGCR antibody, and seronegative IMNM.

Keywords

Idiopathic inflammatory myopathies · Immune-mediated necrotizing myopathy · Anti-SRP antibody · Anti-HMGCR antibody

Immune-mediated necrotizing myopathy (IMNM) is a distinct subgroup of inflammatory myopathy, approximately accounting for 10–30% of all idiopathic inflammatory myopathies (IIM). Clinically, IMNM usually presents with acute onset and manifests as symmetrical proximal muscle weakness. Creatine kinase (CK) levels are almost aways markedly elevated, and muscle biopsy is characterized by the presence of myofiber necrosis, with minimal or absence of inflammatory infiltrates.

IMNM can be classified into three subtypes based on autoantibody positivity: presence of antibodies targeting the signal recognition particle (SRP), presence of antibodies targeting the 3-hydroxy-3 methylglutaryl-CoA reductase (HMGCR), and absence of autoantibodies.

The HMGCR variant is known to have association with statin exposure. Moreover, IMNM can be associated with malignancy, especially in patients with no autoantibodies, and with other connective tissue disorders, such as scleroderma.

Most patients require more than one line of therapy. B cell depletion seems to be an effective treatment for anti-SRP-myositis, and intravenous immunoglobulin (IVIG) for refractory anti-HMGCR subtype [1–5].

Epidemiology

IMNM represents approximately 10–30% of the total of patients with IIM. The prevalence of anti-SRP antibody positivity ranges from 5% to 15% of adult patients, and 4% of youth individuals. On the other hand, anti-HMGCR antibody positivity ranges from 6% to 10% and 1% in adults and children, respectively [3, 6].

This condition is more frequent in the fifth decade of life, with a clear predominance in the female population (ratio 2–3:1). Black race and male sex are associated with increased disease severity.

Autoantibody-negative patients represents 10–12% of cases of IMNM, and they have a markedly increased risk of malignancy. The most common malignancies are gastrointestinal tract adenocarcinoma and small cell and non-small cell lung carcinoma [3, 7].

Etiopathogenesis

Anti-SRP and anti-HMGCR autoantibodies may have a direct toxic effect on muscle cells. It has been suggested that these autoantibodies induce muscle fiber atrophy, impair

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Table 34.1 Epidemiological, clinical, and laboratory features of the IMNM subtypes

	Anti-SRP IMNM	Anti-HMGCR IMNM	Seronegative IMNM
Prevalence			
Adults	5–15%	6–10%	–
Children/youth forms	4%	1%	–
Manifestations			
Weakness	+++	++	++
Muscular damage	+++	++	++
Muscle atrophy and fatty replacement	+++	++	++
Myocarditis	+	–	–
Interstitial lung disease	20–40%	<5%	–
Malignancy	–	–/+	Gastrointestinal tract adenocarcinoma; lung small cell and non-small cell carcinomas
Laboratory			
Creatine kinase levels IU/L	4000–8000	4000–8000	>4000
Risk factors			
Immunogenetic	HLA-DRB1*08:03 DRB1*14:03	DRB1*11:01 adults DRB1*07:01 infants	–
Environmental	Unknown (viral theory)	Statin	–

SRP signal recognition particle, *HMGCR* 3-hydroxy-3-methylglutaryl-coA reductase, *IMNM* immune-mediated necrotizing myopathy

myoblast fusion by decreasing the production of interleukin (IL) 4 and IL-13, and increase levels of reactive oxygen species and proinflammatory cytokines like the tumor necrosis factor and IL-6 [8].

Anti-SRP myopathy is associated with the HLA-DRB1*08:03 and DRB1*14:03 alleles in Japanese and Korean population, respectively [2]. In adults, the class II MHC allele DRB1*11:01 is associated with anti HMGCR-positive IMNM, whereas in infants, it is associated with DRB1*07:01 [8, 9].

The anti-HMGCR variant of IMNM is known to have an association with statin exposure, particularly atorvastatin [1].

Interestingly, the increase in incidence in the months of August to January may indicate a viral infection as a trigger.

Clinical Features

Clinically, IMNM usually presents with acute or subacute onset and manifests as symmetrical proximal muscle weakness, particularly affecting the posterior compartments of the thighs and gluteal regions. Muscle atrophy can be observed. In the rare cases of distal involvement, weakness is more prominent in the dorsal flexors of the foot and the extensors of the fingers.

Anti-SRP IMNM has a similar presentation to anti-HMGCR IMNM, although the first is characterized by more severe and progressive involvement, with a high elevation of CK levels and marked muscular damage in the histopathological findings.

Approximately half of patients with anti-SRP IMNM experience dysphagia at the time of diagnosis, and up to a quarter of patients with anti-HMGCR IMNM.

Interstitial lung disease is detected in 20–40% of patients with anti-SRP myopathy, and in less than 5% of those with anti-HMGCR myopathy. Skin involvement or other extra-muscular features occur in less than 5–10% of patients in both groups [8, 10]. To note, patients with anti-SRP IMNM may have cardiac involvement (myocarditis and/or congestive heart failure), especially in younger patients.

In patients with seronegative IMNM, clinical features are similar to those with seropositive IMNM, usually with no extramuscular symptoms (Table 34.1).

Laboratory

Disease activity is practically always associated with elevated CK levels, usually >4000 UI/l. In young patients, CK levels may be greater than 10,000 IU/L. Other muscle enzymes, such as aldolase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH), are usually elevated as well. IL-17 and IL-23, interferon-beta, toll-like receptors 3 and 7 constitute additional blood biomarkers.

Autoantibody detection is necessary to classify the patients with IMNM. The most commonly techniques used are the enzyme-linked immunosorbent assay (ELISA), line blot assay, dot blot assay, and addressable laser bead immunoassay (ALBIA).

RNA immunoprecipitation (IP) is a sensitive and specific way to indirectly detect the antibodies anti-SRP by identifying the 7S RNA that binds the SRP peptides. However, it is not routinely used in clinical practice.

Interestedly, antibody levels correlate with CK levels and muscle weakness [8, 11].

Histology

A prominent necrosis, regeneration, and myophagocytosis are the characteristic histological findings in IMNM, along with a mild perivascular and endomysial lymphocytic infiltrates (Fig. 34.1). Capillary damage is frequently observed, even without complement deposition [12, 13].

Macrophages are considered the main cells that contribute to the muscle damage, being T cells infiltrates and expression of MHC-I minimal. Nevertheless, 20% of IMNM patients have significant inflammatory cell infiltrates and membrane attack complex (MAC) deposition on the sarcolemma of non-necrotic muscle fibers, and this deposition seems to be more common in anti-HMGCR than anti-SRP patients [3].

The C5b-9 deposition and the expression of MHC class I are associated with a worse prognosis.

The presence of myofibers with fine granular and homogeneous staining of the autophagy marker p62 in the sarcolemma is also common in IMNM (Table 34.2).

Diagnosis and Classification

An adequate clinical history and thorough physical examination are fundamental for the diagnosis of IMNM. Clinical features, blood tests, histopathological findings, as well as the presence of the specific antibodies (anti-SRP or anti-HMGCR) are necessary for the diagnosis and classification [9, 14] (Table 34.3).

- Muscle strength: The medical research council (MRC) scale is the most widely accepted system to measure the muscle strength. Handheld dynamometer can be also use for quantitative evaluation, especially of the arm abductors and hip flexors.
- Laboratory tests: CK levels are useful for the diagnosis and monitoring. In patients with a significant muscle tis-

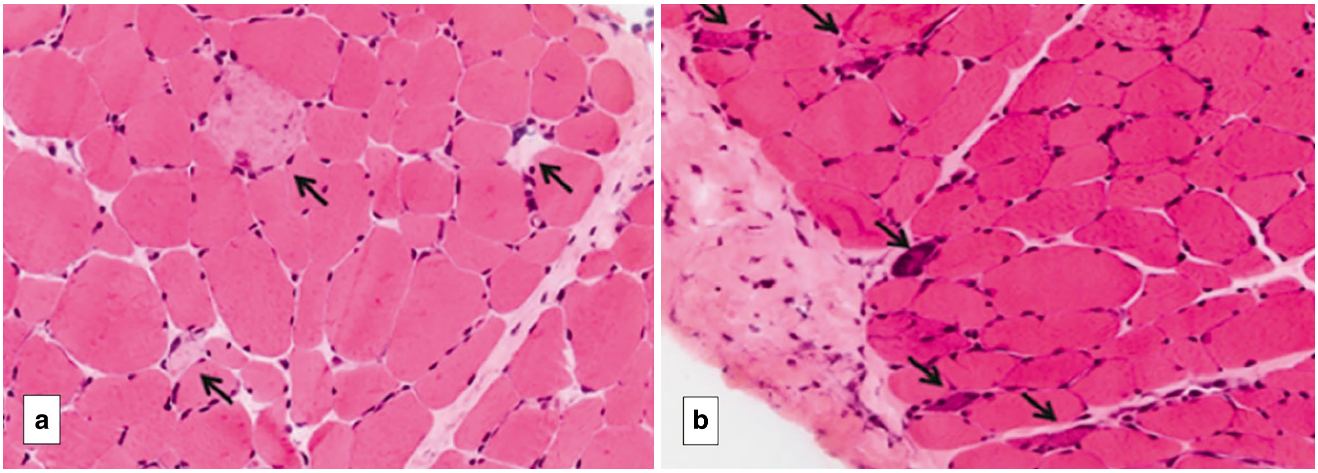

Fig. 34.1 Histopathological findings of immune-mediated necrotizing myopathy. Muscle biopsy slides (H&E in frozen tissue) showing variability in size of muscle fibers with necrotic muscle cells (panel **a**; arrows) and some regenerating basophilic muscle cells (panel **b**; arrows). Absence of significant inflammation

Table 34.2 Pathological findings of the IMNM

Histopathological features
* Extensive necrosis of muscle fibers, with different stages of necrosis and presence of myophagocytes * Endomysial fibrosis may be present in muscle biopsies from patients with chronic IMNM
* MHC class I is seen on the sarcolemma of several fibers with a focal pattern * MHC class II is present on macrophages and capillary endothelial cells
* CD8 T cells are present in the endomysium * CD56-positive myofibers indicate high turnover of muscle fibers * P56 positivity is present in the sarcoplasm of some myofibers * CD31 positivity is present in the endothelial cells of the enlarged capillaries

IMNM immune-mediated necrotizing myopathy, *MHC* major histocompatibility complex

Table 34.3 2017 ENMC criteria for IMNM

	Anti-SRP (22–39%)	Anti-HMGCR (26–50%)	Seronegative IMNM (25–40%)
Clinical criteria	Proximal weakness	Proximal weakness	Proximal weakness
Histopathology criteria – Necrotic fibers – Different stages of: Necrosis myophagocytosis regeneration – Pauci-lymphocytic infiltrate (mainly macrophages)	Muscle biopsy is not required	Muscle biopsy is not required	Muscle biopsy is mandatory
Serologic criteria	Anti-SRP antibody	Anti-HMGCR antibody	No myositis-specific antibody

SRP signal recognition particle, *HMGCR* 3-hydroxy-3-methylglutaryl-coA reductase, *IMNM* immune-mediated necrotizing myopathy, *ENMC* European Neuromuscular Centre

sue replaced by fat and connective tissue, CK variations may be mild. In these cases, imaging techniques are appropriate for activity assessment.

- Muscle Biopsy: As mentioned, it is characterized by the presence of necrosis along with areas of regeneration of muscle fibers with scattered distribution, with minimal or absent inflammatory infiltrates (primarily by macrophages) [10, 14].

In the latest European Neuromuscular Centre (ENMC) criteria for IMNM (2017), a muscle biopsy is not necessary for diagnosis of seropositive patients, but it is mandatory to establish the diagnosis in cases of antibody-negative IMNM.

Complementary Techniques

- Electromyography (EMG): With a sensitivity of more than 90%, this technique may help to choose a suitable muscle for biopsy and disclose the disease extension. Findings include low-amplitude polyphasic units, increased spontaneous activity with fibrillations and positive sharp waves, as well as repetitive complex discharges.
- Magnetic Resonance Imaging (MRI): It provides evidence of both distribution and severity of active disease, and chronic muscular damage. It helps differentiate areas of necrosis, degeneration, and inflammation. T2-weighted sequences show increased signal due to inflammation, which is more typical in acute damage. On the other hand, T1-weighted sequences identify fat replacement in atrophic muscles with muscular damage.

  In anti-SRP patients, MRI usually shows more extensive edema, atrophy, and fatty replacement in the lateral rotator group, more atrophy and fatty replacement in the anterior compartment, and more atrophy in the medial compartment [3].
- Muscular Ultrasound: Although with an inferior sensitivity compared with EMG (82.9% vs 92.4%), this technique can be used to detect inflammatory and chronic involvement [15, 16].

Evaluation of a potential lung involvement with respiratory function test and/or thoracic CT is recommended in anti-SRP patients with respiratory symptoms. Screening for cancer is necessary in seronegative IMNM patients.

Treatment

Currently, treatment recommendations primarily rely on expert opinion and case studies. Treatment should be started as early as possible and tailored based on the severity of the manifestations.

Glucocorticoids (GC) constitute the first line of treatment due to their rapid and broad effectiveness. Prednisone at a dose of 0.5–1 mg/kg/day is recommended, preceded by pulses of methylprednisolone (0.25–1 g iv/day) for 3–5 days in patients with a rapidly progressing weakness, dysphagia, respiratory insufficiency, and other severe organ involvement.

Initiating disease-modifying antirheumatic drugs (DMARDs) at the onset of the disease is also recommended in all the patients, including methotrexate (MTX), azathioprine, mycophenolate mofetil, tacrolimus, ciclosporin, or cyclophosphamide. Mild-moderate forms of both seropositive subtypes usually respond to MTX (DMARD of choice), azathioprine, or mycophenolate.

In refractory or severe cases, intravenous immunoglobulins (IVIG) or rituximab (RTX) should be considered. Moreover, in refractory cases, plasma exchange could be an option, although usefulness is unclear [2, 7] (Table 34.4).

Anti-SRP patients usually have a poorer response to treatment. Rituximab should be early initiated in patients with mild-moderate disease with no response to GC and MTX (or another DMARD), and in patients with severe manifestations (concomitating with IVIG).

After clinical remission, GC dose should be reduced as quick as possible. DMARDs or RTX are maintained for at least 2 years, and, if IVIG have been started, at least 3–6 months of monthly cycles is recommended.

In anti-HMGCR patients, reintroduction of statins should be avoided. Other hypolipidemic agents, as proprotein con-

Table 34.4 2017 ENMC recommendations for IMNM treatment

Induction	*Mild*	– Prednisone 0,5 mg/kg/day – Methotrexate oral/sc 0,3 mg/kg/week (max 20 mg/week in adults) – Other immunosuppressants: Azathioprine or mycophenolate mofetil (in the case of methotrexate intolerance)
	Severe	– Methylprednisolone iv 0,5 to 1 g daily for 3–5 days – Rituximab[a] 1 g administrated at day 1 and day 15 – IVIG[b] 2 g/kg/month (at last 3 months) – Plasma exchange: To consider in very severe and refractory patients
Maintenance		– Taper oral corticosteroids to the minimum dose – Continue methotrexate for at least 2 years of well-controlled disease (taper later at 2,5 mg/week each month) – Continue rituximab (500 mg) every 6 months at least 2 years of well-controlled disease – If IVIG was started, they may be stopped or tapered, as tolerated

SRP signal recognition particle, *HMGCR* 3-hydroxy-3-methylglutaryl-coA reductase, *IMNM* immune-mediated necrotizing myopathy, *IVIG* intravenous immunoglobulins, *ENMC* European Neuromuscular Centre

[a] Rituximab may be used as first-line therapy in patients with moderate-severe anti-SRP IMNM

[b] IVIG is recommended in severe cases of IMNM

vertase subtilisin/kexin type 9 (PCSK9) inhibitors, should be considered.

In addition to pharmacological treatment, physiotherapy and moderate aerobic exercise are crucial for muscle recovery.

Monitoring includes periodical muscle strength and muscle enzymes assessment (mainly CK levels). MRI can be also useful for evaluating the treatment response and disclosing muscle damage during the follow-up.

Prognosis

Around half of the IMNM patients continue having significant weakness after 2 years of treatment, even after a long remission from disease activity. The severity of muscle damage depends on the time from the symptoms and treatment onset, and the disease duration. Early treatment can help to reduce muscle damage.

Anti-SRP positive patients usually have more muscle atrophy and fatty replacement than those with anti-HMGCR positive IMNM, they also have a higher risk of myocarditis.

Iatrogenic effects of immunosuppressants and immunomodulatory treatments can also determine the prognosis [3].

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Granulomatous Myositis

35

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Abstract

Granulomatous myositis (GM) is uncommon, and the demonstration of the granuloma in the muscle biopsy is necessary for its diagnosis. Sarcoidosis constitutes the main etiology, although an increase in the incidence of a GM form associated with inclusion body myopathy is currently recognized. Treatment will be determined by the underlying etiology of the GM. The outcome is variable and, sometimes, unpredictable, and sarcoidosis shows the most favorable response to therapy, based on glucocorticoids.

Keywords

Granulomatous myositis · Sarcoidosis · Inclusion body-myositis · Glucocorticoids

Introduction

Granulomatous myositis (GM) is a disorder characterized by noncaseating granulomatous inflammation of the skeletal muscles. It can configure either an idiopathic entity or accompanying several conditions, such as sarcoidosis, inclusion body myositis (IBM), and other inflammatory and infectious diseases.

Epidemiology

The lack of large studies makes difficult to know the exact prevalence of GM. A large published series found anatomopathological findings of GM in the 0.2–0.6% of the samples, regardless of the clinical symptoms. The onset of the disease occurs between the fifth and sixth decades of life, with a slight female predilection [1, 2].

Etiology

Sarcoidosis is the first cause of GM (50–62%), followed by IBM (38–43%), including an overlapping form of both. Other causes are other immune diseases [1, 3], as well as pharmacological reactions (Table 35.1).

Table 35.1 Etiology of non-necrotizing granulomatous myositis

- Sarcoidosis (all variants) 50–62%
- Inclusion body myositis (including overlap forms with sarcoidosis) 38–43%
- Antimitochondrial antibodies (+/− associated with primary biliary cholangitis) 3–14%
- Myasthenia gravis 0.9–1.0%
- Autoimmune diseases <5%
  - ANCA-associated vasculitis: Granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, microscopic
  - Autoimmune thyroiditis
  - Crohn's disease
- Drugs: Immune checkpoint inhibitors (especially programmed cell death-1 inhibitors) <1%
- Chronic graft-versus-host disease 0.55–2.7%
- Neoplastic (lymphoma) <1%
- Idiopathic 3–5%

ANCA antineutrophil cytoplasmic antibody

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Clinical Manifestations

Symptoms of GM include palpable nodule, weakness, pain, and/or atrophy of the muscles involved, nerve palsy, and dysphagia. Muscle weakness and dysphagia are the most frequent form of presentation, being the first usually bilateral and symmetrical [2].

Sarcoidosis

Only the 0.5–2% of patients with sarcoidosis develop muscular symptoms, and asymptomatic intramuscular granulomas have been reported in about 50% to 80% of sarcoidosis patients [2]. If present, the patients suffer from myalgia, dysphagia, and muscle weakness, characteristically proximal and symmetrical. The presence of granulomas in skeletal muscle in sarcoidosis patients may determine an unfavorable prognosis and a more severe pulmonary and extrapulmonary organ involvement.

Symptomatic patients may present with the following clinical phenotypes: acute myositis, chronic myopathy, palpable muscle nodules, or isolated myalgia.

Patients with the acute myositis phenotype present with severe muscle pain and rapidly progressive proximal limb weakness. Although infrequent, acute myositis typically is one of the first manifestations of sarcoidosis. Serum CK is elevated in most cases, with an average CK level of 3000 U/L.

Chronic myopathy is the most common presentation (67–88%) of the four phenotypes. Patients often present with myalgia and predominantly symmetric proximal lower limb weakness. In contrast to the acute myositis, chronic myopathy usually develops relatively late in the course of sarcoidosis (more than 5 years after the diagnosis). Creatine kinase (CK) is often normal or slightly elevated.

Nodular sarcoid myopathy is the less common phenotype. Patients present with single or multiple palpable nodules that can occur in any skeletal muscles, but more frequently in the lower limbs. The nodules can be painful, but do not cause weakness. Serum CK and electrophysiological studies are normal [1–3].

Inclusion Body Myositis

About 40% of patients with non-necrotizing GM fulfilled the diagnostic criteria of clinicopathologically or clinically defined IBM according to the 2011 European Neuromuscular Center criteria [4]. Moreover, about two-thirds of patients with GM who fulfilled the diagnostic criteria of IBM also had extramuscular involvement that was compatible with systemic sarcoidosis [3]. However, the frequency of IBM in the sarcoidosis population, and vice versa, has not been studied.

In contrast to patients with sarcoid myopathy alone, patients with coexisting sarcoid myopathy and IBM usually present with finger flexor weakness and more frequently dysphagia. Moreover, clinical manifestations related to systemic granulomatosis often precede IBM. As a result, these patients are frequently misdiagnosed as chronic sarcoid myopathy and later found to have IBM after repeat muscle biopsy due to therapy refractoriness [3, 5].

Granulomatous Myopathy with Antimitochondrial Autoantibody

Antimitochondrial antibodies (AMA) may be identified in about 11% of patients with inflammatory myopathy. Moreover, a histopathological finding of GM in patients with AMA-associated myopathy may be shown in 3–14% of patients.

Patients with inflammatory myopathies associated with AMA usually present with a symptom duration of more than 6–12 months before the diagnosis, have muscle atrophy at initial presentation, and have cardiac involvement (arrhythmia, cardiomyopathy, or myocarditis). Serum CK is typically moderately elevated, ranging from 2000 to 3000 IU/L [6, 7].

Granulomatous Myopathy in Other Autoimmune Disorders

GM has been reported in several other autoimmune disorders (Table 35.1), especially in those with histopathological evidence of granulomatous inflammation in their primary affected organs. In a large retrospective study of ANCA-associated vasculitis with abnormal muscle biopsy at diagnosis, granulomas were found in 25% of EGPA patients and 15% of those with GPA [8].

GM has also been described in patients with Crohn disease and Hashimoto thyroiditis.

Granulomatous Myopathy and Myasthenia Gravis with Immune Checkpoint Inhibitors

Many immune-related adverse events have been linked to checkpoint inhibitors, including immune-mediated myopathies, which may manifest as necrotizing myopathy or inflammatory myopathy, including GM, with T or B cell infiltration, some of which were reported with coexisting myocarditis and/or myasthenia gravis [9, 10].

Pathological Features

Biopsy is the gold standard for diagnosis and the presence of granulomas in muscle biopsy, typically with no central necrosis, is mandatory. Focal aggregates of epithelioid histiocytic cells, macrophages, inflammatory lymphocytes, and occasional giant cells of the Langerhans type within the muscle parenchyma, typically located between the muscle cells, constitute the pathological features of the entity (Fig. 35.1). Sarcoplasmic congophilic inclusions can be seen in both IBM and sarcoid myopathy patients and do not favor one over another. Granulomas may be located in either endomysium or perimysium, but this does not distinguish the underlying etiology. In chronic stages, muscle fibers may not be invaded by granuloma, mainly showing atrophy or degeneration [1, 3].

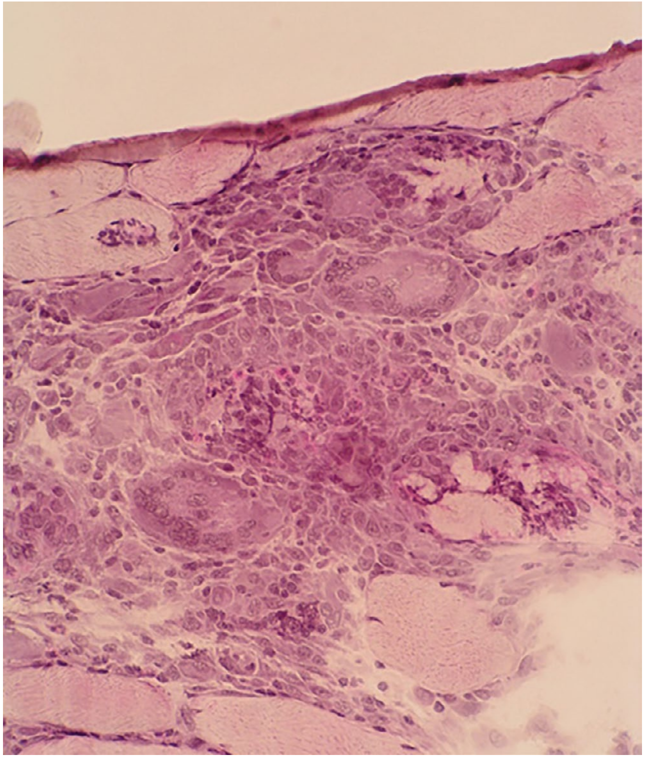

Fig. 35.1 Giant-cells in a muscle biopsy from a patient with a sarcoidosis

Imaging

Imaging techniques have become very useful in assessing muscular involvement in patients with suspected GM, especially in those with nonspecific symptoms or inclusive laboratory/electromyography findings. These may suggest the diagnosis as well as select the most suitable muscle to biopsy. Unlike other myositis or muscular dystrophies, analysis of muscle involvement pattern on imaging is lacking. Muscles affected by GM usually show small foci of T2 hyperintensity with gadolinium enhancement on MRI. Muscle MRI findings in chronic sarcoid myopathy are nonspecific, with proximal greater than distal muscle atrophy and fatty replacement. Patients with nodular sarcoid myopathy have a unique MRI pattern shown as “Dark Star” sign. A “Tiger Man” sign on 18F-FDG PET-CT has also been described in patients with symptomatic sarcoid myopathy, which appears as intense linear uptake in several skeletal muscles throughout the body, corresponding with the location of non-necrotizing granulomas in muscle biopsies [1, 3, 11].

Diagnosis

The diagnosis lies always on the histopathological findings, so a biopsy is essential. Once the diagnosis of non-necrotizing granulomatous myopathy is made, extramuscular granulomatosis, and other signs suggestive of sarcoidosis, should be ruled out. In addition, a thorough search for clinical and pathological clues suggestive of IBM should always be performed even in patients fulfilling the diagnostic criteria for sarcoidosis, and especially in those who are refractory to immunosuppressive therapies.

Searching for AMA, AChR antibodies, thyroglobulin antibodies, TPO antibodies, and ANCA in patients with granulomatous myopathy may help identify the etiology and guide further management [1–3]. A diagnostic algorithm is proposed (Fig. 35.2).

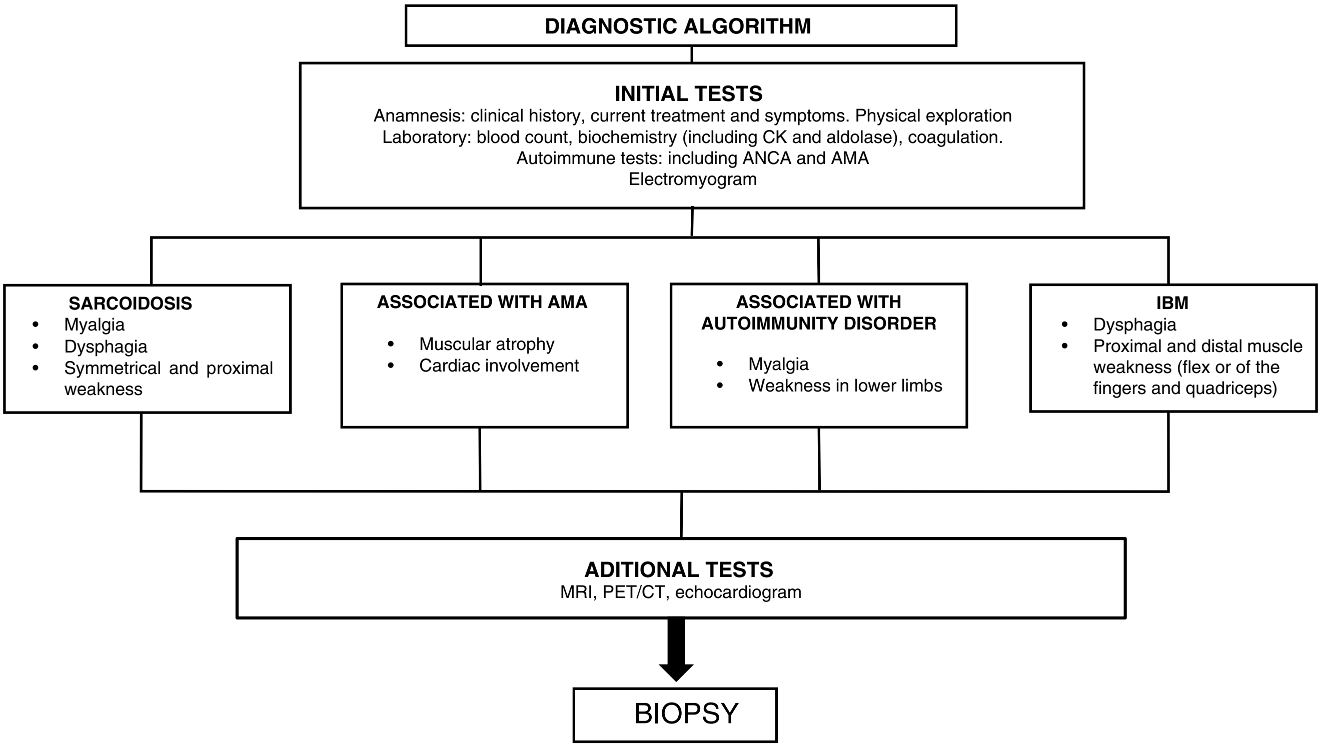
DIAGNOSTIC ALGORITHM
INITIAL TESTS
Anamnesis: clinical history, current treatment and symptoms. Physical exploration
Laboratory: blood count, biochemistry (including CK and aldolase), coagulation.
Autoimmune tests: including ANCA and AMA
Electromyogram
SARCOIDOSIS
Myalgia
Dysphagia
Symmetrical and proximal weakness
ASSOCIATED WITH AMA
Muscular atrophy
Cardiac involvement
ASSOCIATED WITH AUTOIMMUNITY DISORDER
Myalgia
Weakness in lower limbs
IBM
Dysphagia
Proximal and distal muscle weakness (flex or of the fingers and quadriceps)
ADITIONAL TESTS
MRI, PET/CT, echocardiogram
BIOPSY

Fig. 35.2 Proposal for a diagnostic algorithm of the granulomatous myositis. *AMA* antimitochondrial antibodies, *ANCA* Anti-neutrophil cytoplasmic antibody, *IBM* inclusion body myositis, *MRI* magnetic resonance imaging, *PET/CT* positron emission tomography/computed tomography

Therapy

Therapy is based on the underlying disease. In sarcoidosis, oral glucocorticoids (GC) are considered a first-line therapy with a regimen similar to that used in other inflammatory myopathies, usually starting at 0.5–1.0 mg/kg body weight, and with a gradual reduction in dosage. Refractory cases have been shown to improve with the addition of low-dose methotrexate. Cyclophosphamide, cyclosporine, and azathioprine, have also been used, with mixed outcomes. The response to immunosuppressive therapy varies greatly. Some patients respond dramatically, yet others experience progression of muscle weakness and severe disability. Therapy is usually efficacious in patients with nodular lesions, but frequent relapse is reported. Treatment with hydroxychloroquine is usually effective in sarcoidosis patients with only myalgia [1–3].

Several immunotherapeutic strategies have been tried in inclusion body myositis. However, none have shown robust sustained efficacy or effectively slowed the rate of disease progression. Only intravenous immunoglobulin has shown to be effective in some patients with dysphagia [12]. Attention and hope have now shifted to two drugs (sirolimus and a monoclonal antibody against the KGLR1) that are currently tested in ongoing trials [13].

Recognizing the clinical and pathological features of IBM will help to distinguish it from or associated with sarcoid myopathy, and potentially spare a subset of these patients from unnecessary exposure to immunosuppressive therapies, especially in the absence of active sarcoidosis [3, 14].

Prognosis

Only a little information is available on the long-term course and prognosis of GM, and the clinical outcome varies widely. While good response is obtained with corticosteroids in acute symptomatic cases, poor response is the rule in chronic patients. There are also differences among the idiopathic forms and sarcoidosis-related cases, with a better outcome observed in the latter. The presence of IBM clinical and pathological findings, as well as GM with AMA and heart involvement, makes the outcome frequently unfavorable [1, 2].

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Eosinophilic Myositis

36

Albert Selva-O'Callaghan, Ernesto Trallero-Araguás, and Jose Milisenda

Abstract

Eosinophilic myositis (EM) constitutes a group of rare, clinically, and pathologically heterogeneous disorders characterized by eosinophil infiltration of skeletal muscle. Most cases have no known etiological factor and are considered idiopathic. EM should be distinguished from dermatomyositis and other systemic diseases, such as eosinophilic granulomatosis with polyangiitis or hypereosinophilic syndrome. Idiopathic EM can be classified into three subtypes: focal EM, eosinophilic polymyositis, and eosinophilic perimyositis. Recently, a refined classification delineated four phenotypes, including eosinophilic myofasciitis and the classical form of eosinophilic fasciitis, considering these disorders a clinical-pathological continuum from the muscle to the fascia and skin. Pathological studies are mandatory to differentiate and diagnose these entities.

Keywords

Eosinophilic myositis · Focal eosinophilic myositis · Eosinophilic perimyositis · Inflammatory myopathy · Eosinophilic major basic protein · Diagnostic criteria

Description of the Disease

Eosinophilic myositis (EM) is a rare form of inflammatory myopathy with muscle eosinophilic infiltration [1, 2]. Frequently, although not always, it coexists with peripheral eosinophilia (>500/μl). It can be focal or diffuse, idiopathic, or secondary to other entities [3], such as dystrophies (i.e., calpainopathy, the so-called LGMD 2A) [4–7], idiopathic hypereosinophilic syndrome [8], eosinophilic granulomatosis with polyangiitis [9], or allergic disorders [10]. Some authors have linked the EM to other forms of eosinophilic diseases, such as eosinophilic fasciitis [2, 11, 12], establishing a clinical-pathological continuum from the muscle to the fascia and skin, although a pathogenic link between both entities has not been reported until now. In some cases, eosinophilic infiltrate invades the intermuscular fascia generating a specific form of muscle involvement that may be defined as perymiositis [2], in these cases the muscle is constricted due to the thickening and eosinophilic infiltration of the fascia and is not a true infiltrate of the muscle fibers (Fig. 36.1). No specific autoantibodies have been associated

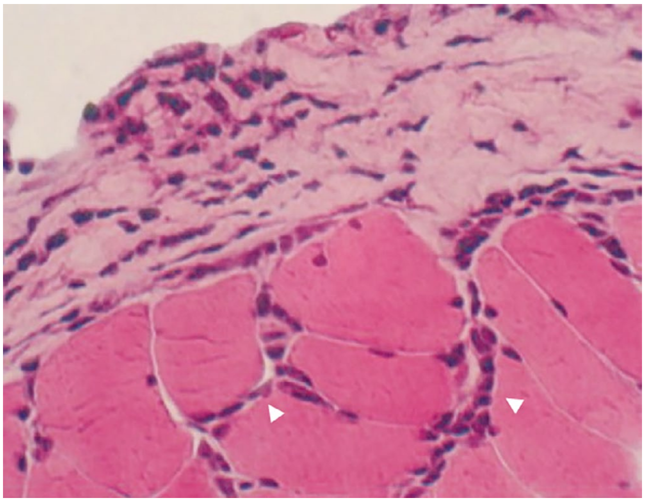

Fig. 36.1 Eosinophilic perimyositis (arrowhead)

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with EM. Focal forms tend to be more benign than diffuse, affecting mainly extraocular muscles or specific areas of the body, preferentially extremities, lower limbs, hand, and thigh [13–16].

Pathogenesis is unknown, although eosinophil activation and release of toxic granular proteins, specifically the eosinophilic major basic protein, have been associated as a cause of muscle damage. The currently proposed criteria [2] has been used by physicians during the last decade (A), which include the phenotypes: focal eosinophilic myositis, diffuse eosinophilic myositis, and eosinophilic perimyositis (see Fig. 36.2). Recently [12] a retrospective study on 30 patients diagnosed with idiopathic eosinophilic myositis (see inclusion criteria, B) allow for a more refined classification, which includes four phenotypes: focal eosinophilic myositis, diffuse eosinophilic myositis, eosinophilic myofasciitis, and the classical eosinophilic fasciitis (see Fig. 36.3) that only the time goes by may confirm its utility.

Main signs and symptoms, laboratory findings, and serological markers are collected in Tables 36.1 and 36.2.

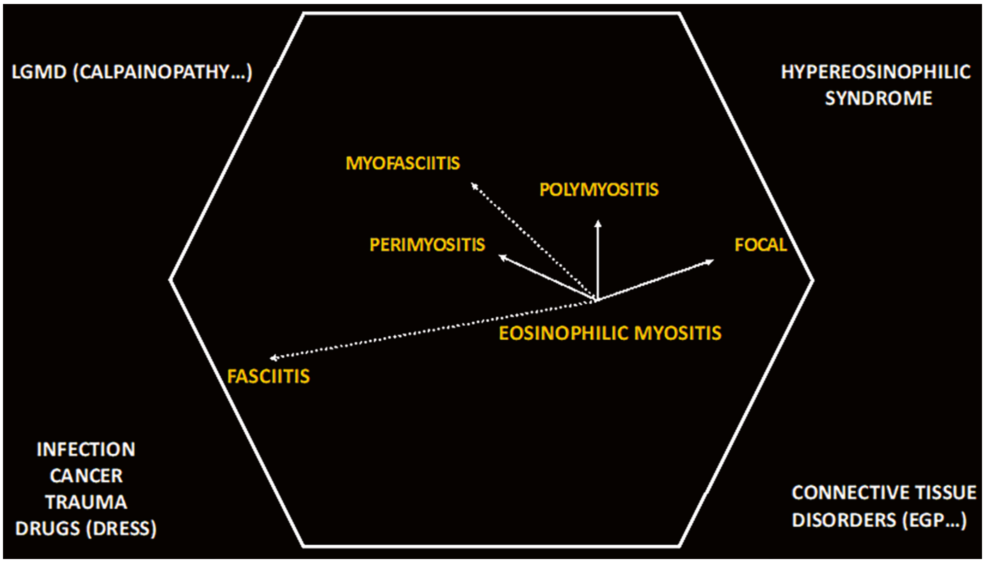
LGMD (CALPAINOPATHY…)
HYPEREOSINOPHILIC SYNDROME
MYOFASCIITIS
POLYMYOSITIS
PERIMYOSITIS
FOCAL
EOSINOPHILIC MYOSITIS
FASCIITIS
INFECTION
CANCER
TRAUMA
DRUGS (DRESS)
CONNECTIVE TISSUE DISORDERS (EGP…)

Fig. 36.2 Eosinophilia-associated myopathy phenotypes (*see refs.* [2, 12]). (DRESS: drug reaction with eosinophilia and systemic symptoms; EGP: eosinophilic granulomatosis with polyangiitis, LGMD: limb-girdle muscle dystrophy)

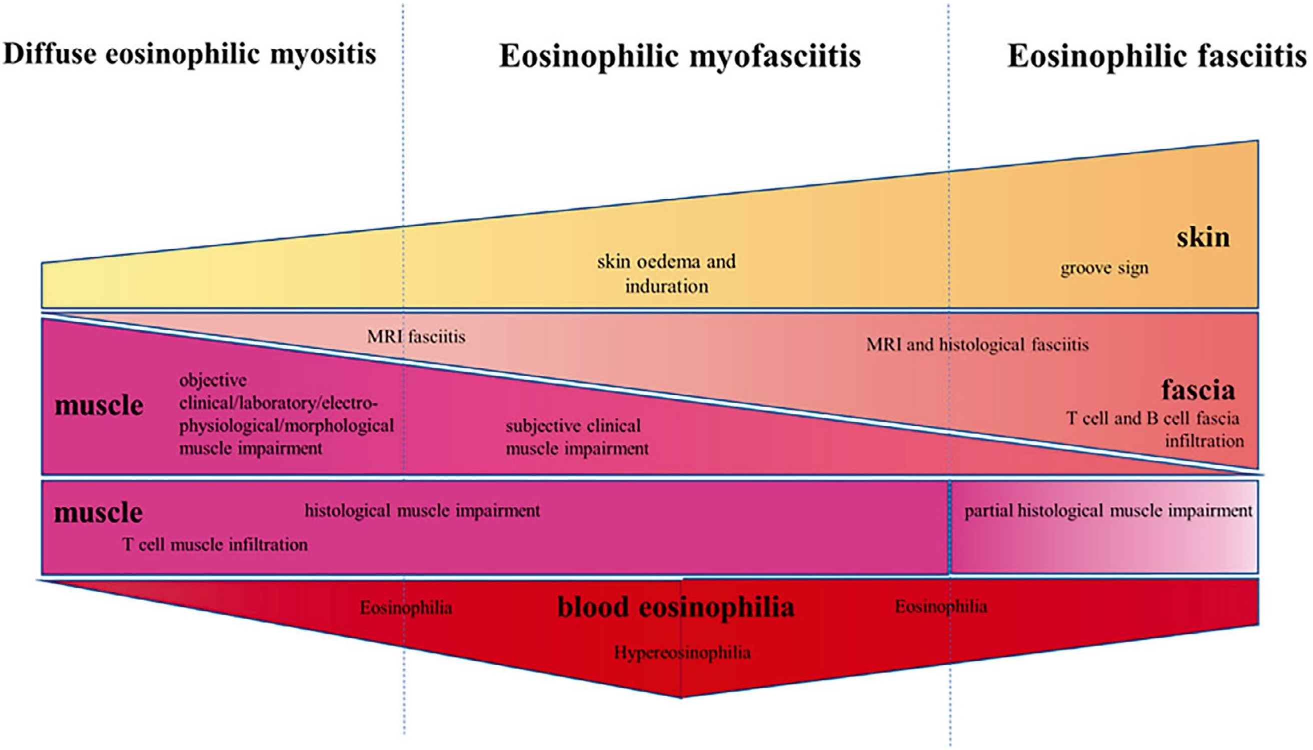
Diffuse eosinophilic myositis
Eosinophilic myofasciitis
Eosinophilic fasciitis
skin oedema and induration
skin
groove sign
MRI fasciitis
MRI and histological fasciitis
muscle
objective clinical/laboratory/electro-physiological/morphological muscle impairment
subjective clinical muscle impairment
fascia
T cell and B cell fascia infiltration
muscle
histological muscle impairment
T cell muscle infiltration
partial histological muscle impairment
Eosinophilia
blood eosinophilia
Eosinophilia
Hypereosinophilia

Fig. 36.3 Schematic representation of the clinic-pathological continuum from diffuse eosinophilic myositis to eosinophilic fasciitis (*from Fermon C* et al*, ref* [12])

Table 36.1 Signs/symptoms related to eosinophilic myositis. (*Percentages are retrieved from ref.* [3])

Focal eosinophilic myositis
- Swelling (76.5%)
- Muscle edema
- Inflammatory signs
- Pain (58.8%)
- Weakness (of the hand or limb when involved) (23.5%)
- Diplopia (when extraocular muscles are involved)

Diffuse eosinophilic myositis
- Proximal muscle weakness (difficulty rising from a chair, raising both arms, combing the hair, or taking a shower) (58.3%)
- Muscle pain (58.3%)
- Dysphagia
- Myocardial involvement (11%)
- Myalgia (>50%)

Eosinophilic perimyositis
- Weakness (18.8%)
- Pain (68.8%)

Table 36.2 Laboratory findings and serologic markers. (*Percentages are retrieved from ref.* [3])

- Elevated serum levels of creatine kinase and aldolase (two- to ten-fold)
  - *Focal eosinophilic myositis* (50%)
  - *Diffuse eosinophilic myositis* (90.6%)
  - *Eosinophilic perimyositis* (16.7%)
- Peripheral eosinophilia >500/µl
  - *Focal eosinophilic myositis* (62.5%)
  - *Diffuse eosinophilic myositis* (84.8%)
  - *Eosinophilic perimyositis* (75%)
- Elevated values of acute phase reactants (ESR)
  - *Focal eosinophilic myositis* (25%)
  - *Diffuse eosinophilic myositis* (27.8%)
  - *Eosinophilic perimyositis* (26.7%)
- Next-generation sequencing to rule out LGMD
- Negativity to specific and associated myositis autoantibodies
- Clonal eosinophilia analysis in order rule out lymphocytic (activated T cells and overproduction of IL-5) and myeloid hypereosinophilic syndrome (FIP1L1 platelet-derived growth factor receptor alpha (PDGFRA) fusion gene) when suspected

(A) Proposed Diagnostic criteria in Patients with Suspected Eosinophilia-Associated Myopathy [2]

Focal Eosinophilic Myositis

Major

1. Pain and calf swelling (other muscles can be affected).
2. Deep mononuclear cell infiltration (eosinophilic or not), with muscle fiber infiltration and necrosis on muscle biopsy.

Minor

Elevated serum levels of creatine kinase and aldolase (two- to ten-fold).
MRI or electromyographic evidence of focal myositis.
Absence of systemic illness.
Peripheral eosinophilia >500/µl.

Deep vein thrombosis, cellulitis, and parasitic infections must be excluded.

The presence of two major criteria, or one major criterion and all three minor criteria establishes the diagnosis.

Diffuse Eosinophilic Myositis

Major

1. Proximal weakness affecting limb-girdle muscles, sometimes severe.
2. Widespread deep infiltration of eosinophils into muscle, with eosinophilic cuffing on histology study. Myonecrosis and endomysial inflammation are usually present. In the absence of eosinophil infiltration, MBP deposition should be demonstrated by specific immunostaining.

Minor

Elevated serum levels of creatine kinase and aldolase (usually high >10 ULN).
Peripheral eosinophilia >500/µl.
Systemic illness with frequent cardiac involvement.
Corticosteroids are needed.

Hypereosinophilic syndrome, T cell clonality, dermatomyositis, vasculitis (Churg–Strauss syndrome), drugs, LGMD (Becker muscular dystrophy, calpainopathy, and sarcoglycanopathy), and parasitic infections must be excluded.

Presence of both major criteria or one major criterion and two minor criteria establishes the diagnosis.

Eosinophilic Perimyositis

Major

1. Myalgia, proximal mild weakness.
2. Eosinophilic infiltrate confined to fascia and superficial perimysium, absence of myofiber necrosis.

Minor

Absence of systemic manifestations.
Normal creatine kinase, aldolase levels slightly elevated (less than 2–3 ULN).
Peripheral eosinophilia >500 µl.

Toxic oil syndrome, myalgia–eosinophilia, exposure to other inorganic or organic substances should be excluded.

Presence of both major criteria and major criterion number 2 plus two minor criteria enable the diagnosis.

LGMD: limb-girdle muscle disease; MRI: magnetic resonance imaging; ULN: upper limit of normal.

(B) Refining Idiopathic Eosinophilic Myositis Classification [12]

Considering Muscle Biopsy

- Eosinophilic infiltration within the epimysium and/or the perimysium and/or the endomysium
- Pathological features of myositis, which consists of at least two of the following criteria
  Positive MHC type I (MHC-I) immunostaining; inflammatory infiltrate within the perimysium and/or the endomysium
  Necrotic myofibers

Clinical Forms

Focal myositis
Diffuse myositis
  - Diffuse and objective muscle weakness, myogenic EMG, MRI myositis

Myofasciitis
  - myalgia and subjective muscle impairment, muscle, and fascia involvement

Short Paragraph on Therapy and Prevention

No prevention strategies exist given the lack of knowledge about the etiopathogenesis of EM, and there is no consensus regarding which will be the best therapeutical approach for these eosinophilic-associated muscle disorders. However, from clinical practice, first-line therapy includes glucocorticoids (1 mg/kg/day), which may be combined with other immunosuppressive drugs depending on the severity of the disease. Focal myositis usually has a good prognosis with full recovery after a short bout of glucocorticoids. Diffuse forms occasionally may be severe, especially if internal organs (i.e., myocardium) are involved. Cyclophosphamide, azathioprine, methotrexate, or mycophenolate mofetil may be introduced as well as anti-CD20 monoclonal antibodies (rituximab) in some circumstances. Tyrosine kinase inhibitors (imatinib mesylate 100-400 mg/day) and JAK inhibitors (ruxolitinib 30 mg/day, tofacitinib 5 mg/12 h) have also been described as useful therapies in the context of hypereosinophilic syndrome. Lastly, some eosinophil-targeting therapies, such as monoclonal antibodies against IL-5 (mepolizumab and reslizumab), and against IL-5 receptor (benralizumab) could be useful in refractory scenarios.

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Eosinophilic Fasciitis

37

Albert Selva-O'Callaghan, Iago Pinal-Fernández,
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Abstract

Eosinophilic fasciitis (EF) is an uncommon scleroderma-like syndrome with an unknown etiology and pathogenesis. Painful swelling with progressive induration and thickening of the skin and soft tissues of the limbs and trunk are the clinical hallmarks of the disease. Peripheral blood eosinophilia, hypergammaglobulinemia, and elevated erythrocyte sedimentation rate are the main laboratory findings. Full-thickness wedge biopsy of the clinically involved skin is essential for establishing an accurate diagnosis. Differential diagnosis includes systemic sclerosis and other fasciitis syndromes caused by substances, such as L-tryptophan, myalgia-eosinophilia, and toxic oil syndrome. Diagnosis of EF can be established by clinical, laboratory, and histological findings. Tentative diagnostic criteria have been previously reported, although universally accepted criteria are lacking. Herein we update previously reported diagnostic criteria considering data published in the last decade. Corticosteroids are effective in the treatment of EF. Some patients improve spontaneously.

Keywords

Eosinophilic fasciitis · Diagnostic criteria · Classification · MRI · Perimyositis · Eosinophilia · Fasciitis

Description of the Disease

Eosinophilic fasciitis (EF) is a scleroderma-like disorder first described by Shulman [1] in 1974. This skin fibrosis disorder is relatively uncommon and occurs in a sporadic rather than epidemic form. It can be localized, involving one extremity, or less frequently generalized, affecting the four extremities, the trunk, and abdomen, causing ventilatory restriction in some cases. EF is characterized by induration of the skin, peripheral eosinophilia, and hypergammaglobulinemia. The onset of the disease is usually abrupt and, in some cases, follows excessive physical activity. Associated hematological diseases and autoimmune thyroid disorders have been reported in some series [2, 3]. Visceral and extracutaneous involvements in FE are unusual [4, 5].

Painful and erythematous swellings of the affected extremities are the main cardinal clinical features. Edema is progressively replaced by thickening of the skin, which is firmly bound to the underlying tissue. "Peau d'orange" appearance (Fig. 37.1) and the "groove" sign (Fig. 37.2) [6], a longitudinal depression in the skin along the course of blood vessels, are characteristic findings in these patients. Skin induration can lead to joint contractures with limited mobility. EF can easily be differentiated from systemic sclerosis because of the absence of sclerodactyly, microstomy, and telangiectasias. Raynaud's phenomenon is usually absent and the capillaroscopy is normal.

A full-thickness wedge biopsy of the involved skin usually reveals characteristic findings (Fig. 37.3). The fascia muscularis shows accumulation of lymphocytes, macro-

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phages, and plasma cells. Paradoxically, eosinophils are not always found in the tissue affected. The fascia muscularis is usually 2–15 times the thickness of normal fascia and is firmly adherent to the subjacent skeletal muscle. The dermis and epidermis are usually normal. The epimysium near the fascia and perimysium among muscle fibers are often inflamed given the so-called perimyositis that may be also seen in some cases of eosinophilic myositis [7].

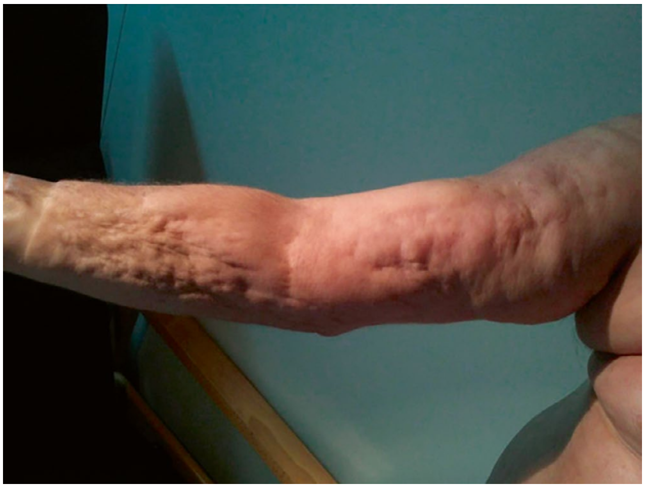


Fig. 37.1 Peau d'orange

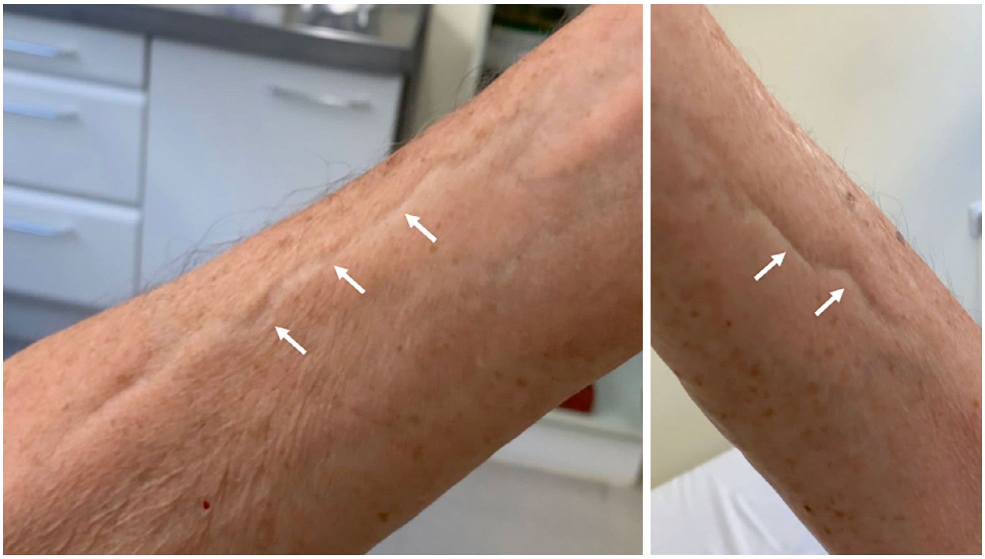
Diagnostic Criteria

Universal diagnostic criteria for diagnosing eosinophilic fasciitis are still lacking. Nevertheless, the previously proposed criteria from 2014 [17] seem to have been accepted by the medical community and are frequently used by clinicians. The PET/CT is a useful technique to identify fascial involvement and we propose adding it as a new minor criterion to our classification. New series including a large number of patients with eosinophilic fasciitis are now included in the tables of signs and symptoms (Table 37.1) and laboratory findings (Table 37.2), although they do not seem to modify the previously proposed criteria.

Main image findings in patients with eosinophilic fasciitis are shown in Table 37.3.

Proposed criteria for the diagnosis of patients with eosinophilic fasciitis [17].

Fig. 37.2 Groove sign (forearm, arrows)



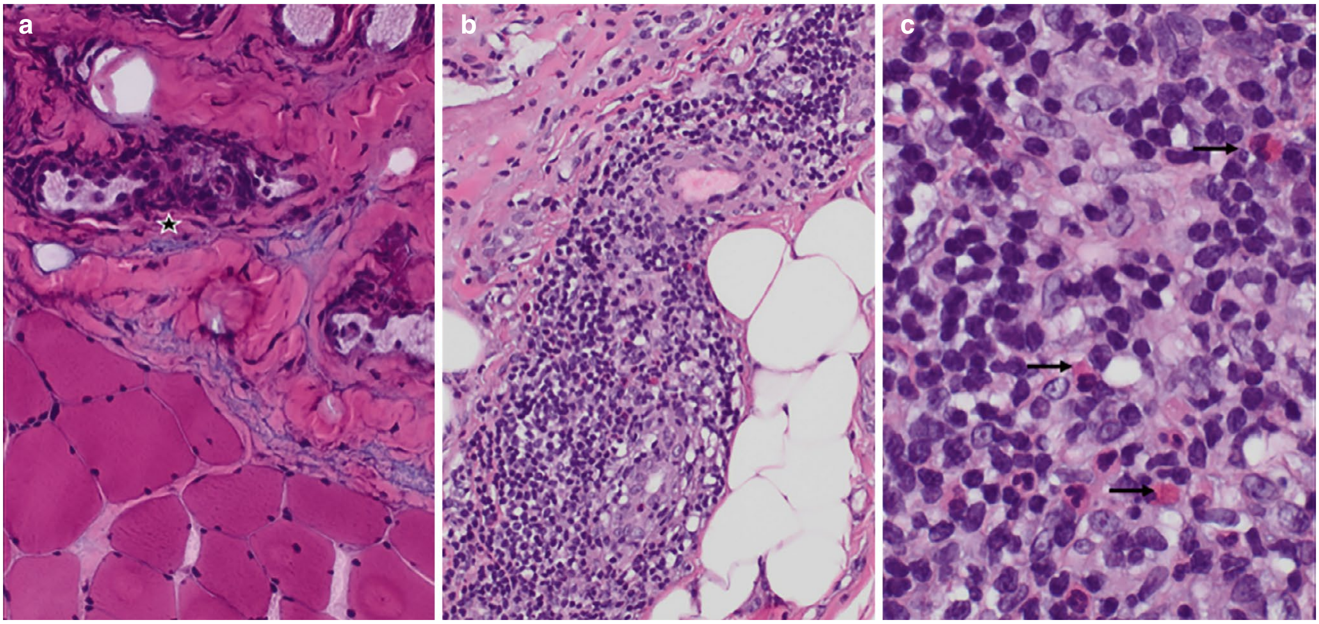


Fig. 37.3 Cross section of muscle and fascia, H&E staining (**a**–**c**). Perivascular inflammatory infiltrate is observed in the epimysium (**a**, asterisk), as well as in the fascia (**b**), along with the presence of some eosinophils (**c**, arrows)

Table 37.1 Main signs and symptoms in patients diagnosed with eosinophilic fasciitis. Numbers express percentages (%)

References	Antic [4]	Lakhanpal [2]	Trallero [8]	Endo [9]	Pehl [6]	Mango [10]	Chaigne [11]
Skin induration	100	96	100	100	88	–	49
Localized[a]	–	60	30	74	69	63	70
Diffuse[b]	–	40	70	26	31	37	30
Erythema	100	–	10	–	–	–	–
Pitting oedema	82	44	70	–	50	–	45
Hyperpigmentation	9	–	30	–	12	–	–
Facial oedema	9	6	0	–	-	–	7
Groove sign	18	–	40	–	38	29	21
Peau d'orange	–	21	20	–	–	25	23
Contractures	27	56	40	–	–	–	–
Fever	–	–	20	–	6	–	–
Weight loss (> 15%)	–	–	40	–	43	–	–
Ventilatory restriction	0	7	40	–	–	–	–
Perimyositis	–	7	6	–	–	–	–
Raynaud's	0	2	10	–	–	–	–
Sclerodactylia	9	0	0	–	–	–	–
Pruritus	–	–	30	–	–	–	–
Arthritis	–	40	20	–	31	10	–

[a] Localized: either lower extremities or forearms, asymmetric

[b] Diffuse: skin induration of trunk, abdomen, and four extremities

Table 37.2 Laboratory findings in patients diagnosed with eosinophilic fasciitis

References	Antic [4]	Lakhanpal [2]	Trallero [8]	Endo [9]	Pehl [6]	Mango [10]	Chaigne [11]
Blood eosinophilia	64	63	100	92	81	5	89
Hypergammaglobulinemia	18	34	40	50	50	29	13
ANA	18	6	10	22	–	10	–
Autoantibodies	0	4	0	–	–	2–18	–
Aldolase	–	–	40	–	–	31	–
Cytopenias	9	2	10	–	–	–	–
Thyroid dysfunction	1	-	10	–	–	–	–
Elevated ESR/CRP	64	29	–	74	78	25	38

Eosinophilia: > 0.5 × 10^9/l
ANA antinuclear antibodies, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, Numbers are expressed in percentage (%)

Table 37.3 Diagnostic imaging in eosinophilic fasciitis

Magnetic resonance imaging (MRI) [12]
Thickening of superficial muscle fascia (40.7%)
Thickening of deep muscle fascia (35.4%)
Edema (24.5%)
No findings suggestive of eosinophilic fasciitis (4.8%)
Ultrasound (US) [10]
Thickening of skeletal muscle (13.2%)
Thickening of the superficial/deep fascia (24.5%)
Thickening of subcutaneous tissue (7.54%)
No findings suggestive of eosinophilic fasciitis (13.2%)
PET/CT [13–16]
Subcutaneous and fascial hypermetabolism (especially when EF is an immune-related adverse event in those patients treated with check point inhibitors)

Major Criteria

1. Swelling, induration, and thickening of the skin and subcutaneous tissue that is symmetrical or nonsymmetrical, diffuse (extremities, trunk and abdomen), or localized (extremities).
2. Fascial thickening with accumulation of lymphocytes and macrophages with or without eosinophilic infiltration (determined by full-thickness wedge biopsy of clinically affected skin).

Minor Criteria

1. Eosinophilia >0.5 × 10^9/L.
2. Hypergammaglobulinemia >1.5 g/L.
3. Muscle weakness and/or elevated aldolase levels.
4. Groove sign and/or *peau d'orange*.
5. Hyperintense fascia on MRI T2-weighted images.
6. ^{18}F-PET/CT (subcutaneous and fascial hypermetabolism).

Exclusion Criteria: Diagnosis of Systemic Sclerosis

Presence of both major criteria, or one major criterion plus two minor criteria, establishes the diagnosis of eosinophilic fasciitis.

Therapy and Prevention

Glucocorticoids are the first-line therapy for eosinophilic fasciitis, usually at 1 mg/kg/day dose and with a progressive drug tapering over time. In patients with insufficient response to glucocorticoids, relapse of the diseases or adverse events related to this therapy (i.e., osteoporosis, diabetes,…) combination with other immunosuppressive agents, such as methotrexate (on a weekly basis), mycophenolate mofetil [18], or intravenous immunoglobulin (monthly), may help to improve the clinical manifestations of the disease. Tocilizumab, infliximab, and Janus kinase inhibitors have all been used sporadically in refractory cases [19–21]. IL-5 seems to play a role in the activation of eosinophils, and for this reason it has been proposed to treat refractory cases of eosinophilic fasciitis with anti-IL5 monoclonal antibodies (mepolizumab) [22] or anti-IL5 receptor monoclonal antibodies (benralizumab) [23]. No prevention strategies exist for patients with eosinophilic fasciitis.

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Part IV

Other Immune-Mediated Systemic Diseases

Sarcoidosis

38

Juan Mañá and Adriana Iriarte

Abstract

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. The available evidence suggests that the disease results from an exposure of genetically susceptible hosts to specific and persistent environmental and occupational agents, which causes a heightened innate immune response in the involved organs leading to granuloma formation. Sarcoidosis usually presents with bilateral hilar lymphadenopathy, pulmonary, cutaneous, and ocular involvement, although any organ can be affected. Although they are less frequent, neurosarcoidosis and cardiac sarcoidosis require a special consideration. The diagnosis is based on a compatible clinical and radiological picture, demonstration of noncaseating granulomas with negative cultures for mycobacteria and fungus, and exclusion of other granulomatous diseases. The finding of granuloma at biopsy is not specific for sarcoidosis. The differential diagnosis of granulomatous diseases varies according to the involved organ. Tuberculosis and sarcoid reaction secondary to cancer should be excluded. In general, an acute onset, particularly Löfgren's syndrome, has a good prognosis, while an insidious presentation heralds a chronic disease. A significant proportion of patients with sarcoidosis follows a spontaneous resolution without treatment. Corticosteroids should be administered when symptomatic and severe and progressive disease involves major organs, such as lungs, eyes, heart, and central nervous system. Several drugs, such as methotrexate, hydroxychloroquine, and infliximab, may be useful as alternative therapies in cases refractory to corticosteroid treatment.

Keywords

Sarcoidosis · Diagnosis of sarcoidosis · Löfgren's syndrome · Neurosarcoidosis · Cardiac sarcoidosis · Prognosis of sarcoidosis · Treatment of sarcoidosis

Sarcoidosis is a multisystem disease of unknown etiology characterized by the accumulation of T lymphocytes, mononuclear phagocytes, and noncaseating granulomas in the affected organs. It frequently presents with bilateral hilar lymphadenopathy (BHL), and pulmonary, cutaneous, and ocular involvement, although any organ can be affected. The diagnosis requires the exclusion of other granulomatous diseases, particularly tuberculosis (TB) and tumor-related sarcoid reaction [1].

Epidemiology

Sarcoidosis occurs throughout the world. However, because of the lack of a precise definition and the fact that some cases are asymptomatic, the true incidence is unknown. The prevalence ranges from 10–40 per 100,000 in the United States and Europe. Most of patients are young and middle-aged adults with a slight predominance in women, more evident in Löfgren's syndrome (LS). Afro-American and Asian Indians have more severe disease, while asymptomatic cases are more common in Caucasian. LS is more frequent in the Northern European countries and Spain, and predominates during the spring months [1, 2].

Etiology

The cause of sarcoidosis is not known. The available evidence suggests that the disease results from an exposure of genetically susceptible hosts to specific and persistent envi-

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ronmental and occupational agents, which causes a heightened innate immune response in the involved organs [3]. Multiple studies have focused on the relationship between sarcoidosis and human leukocyte antigen phenotypes. Genetic factors are important in defining the pattern of disease presentation and prognosis. Most of the sarcoidosis genetics associations were found with genome-wide association study (GWAS) investigations. In particular, a common haplotype of the C-C chemokine receptor 2 gene and HLA-DRB1*0301 are not only associated with increased susceptibility but also with disease resolution in European Löfgren's syndrome patients [4]. Although some studies have speculated on a role for microbial antigens, particularly *Mycobacterium spp* and *Cutibacterium acnes*, in the etiology of the disease, to date there is no evidence that sarcoidosis is caused by an infectious agent [1].

Immunopathogenesis

Sarcoidosis characterizes by a Th1 immunological response. Initially, there is accumulation in the involved organs of activated CD4+ T lymphocytes and mononuclear phagocytes, which release IL-2, IFN-γ, and other cytokines, leading to the formation of noncaseating granulomas. Granulomas may resolve spontaneously or lead to chronic disease including fibrosis with permanent tissue damage. TNF-α plays a role in the inhibition of apoptosis in the granuloma, which contributes to the persistence of inflammation and evolution to fibrosis [1, 4].

Clinical Presentation and Organ Involvement

Sarcoidosis is occasionally discovered by chance in an asymptomatic individual, usually as BHL on chest radiograph or thoracic computed tomography (CT) [5]. The onset of sarcoidosis may be acute or insidious. Acute sarcoidosis develops over a period of weeks or a few months, and it usually heralds a good prognosis. It is characterized by mild constitutional symptoms, such as fatigue, malaise, low-grade fever, arthralgias, and respiratory symptoms. One of the most typical forms of acute sarcoidosis is LS. It consists in the association of erythema nodosum with BHL, sometimes with pulmonary involvement, on the chest radiograph. Some patients present only a periarticular ankle inflammation without erythema nodosum, which has been considered a clinical variant of LS. Polyarthralgias, low-grade fever, anterior uveitis, and transient unilateral facial paralysis may be present as well [2]. On the other hand, an insidious onset for several months is usually associated with respiratory complaints without constitutional symptoms, or with symptoms referable to organs other than the lung. It rather correlates with a chronic course and permanent organ damage [6–8].

Pulmonary Sarcoidosis

Pulmonary involvement occurs in 90% of cases, so 10% of patients have isolated extrapulmonary sarcoidosis (stage 0). The inflammatory process is mainly located on alveoli, small bronchi, and small blood vessels and predominates on the upper lung zones. Patients may be asymptomatic or present dry cough and dyspnea with exercise. Associated bronchial hyperreactivity may be present. Hemoptysis is rare. Rales are not frequent. Table 38.1 shows the classical radiological stages of sarcoidosis. Hilar bilateral and right paratracheal adenopathy and reticulonodular infiltration with upper lung zones predominance is the most typical pattern. Atypical radiological findings include large nodules, alveolar infiltrates, hilar calcification, pleural effusion, and pneumothorax [9–11]. External compression by enlarged hilar adenopathies or endobronchial involvement may cause distal atelectasis. The evolution to fibrosis may cause large airway distortion with severe dysfunction and pulmonary hypertension [12].

Skin

The skin is the second organ most frequently involved in sarcoidosis after the lung. Specific (granulomatous) skin lesions are present in 9–37% of patients with sarcoidosis. The most

Table 38.1 Chest radiograph stages in pulmonary sarcoidosis[a]

	% at onset	% with resolution
Stage 0: Normal chest radiograph	<10%	
Stage I: BHL without pulmonary involvement	50%	65%;<10% progress to pulmonary involvement
Stage II: BHL with pulmonary involvement	30%	20–50%
Stage III[b]: Pulmonary involvement without BHL	10–15%	<20%

[a] Classification based on chest radiograph. Although thoracic CT may suggest a different stage, it is not necessary to change the criteria since these tests are indicated only in a limited number of patients

[b] Stage III may be subclassified in stage IV, which includes cases with advanced pulmonary fibrosis (hilar retraction, coarse linear opacities, honeycombing, bullae, emphysematous changes, architectural distortion, and pulmonary hypertension)

common are maculopapular lesions (particularly over the knees), infiltration of old scars, subcutaneous nodules, plaques, and lupus pernio. The last two are associated with chronic sarcoidosis [13].

Ocular

Ocular involvement occurs in 15–20% of patients. Since it may be asymptomatic, slit-lamp and ophthalmoscope examinations should be performed on every patient with sarcoidosis. Fluorescein angiography may be indicated if posterior uveitis is suspected. The most frequent findings are anterior or posterior uveitis, choroidoretinitis, periphlebitis, papilledema, and retinal hemorrhages. Conjunctivitis, lacrimal gland involvement, and keratoconjunctivitis sicca may be present as well [2, 6].

Reticuloendothelial System

Peripheral lymphadenopathy involving the cervical, supraclavicular, epitroclear, axillary, and inguinal nodes may be present. In addition to intrathoracic, mesenteric chain and retroperitoneal lymph nodes may be present as well. Splenic involvement is frequent, although splenomegaly occurs only in 5–10% of cases and may result in pancytopenia. Multiple low-attenuation nodules may be seen in the spleen on CT. Bone marrow involvement is rare [2, 6].

Liver

Liver involvement with presence of periportal granulomas at biopsy is very frequent in sarcoidosis. Mild hepatomegaly with slight cholestasis occurs in 20–30% of patients. Severe chronic cholestasis syndrome, portal hypertension, and Budd-Chiari syndrome are rare. Multiple low-attenuation nodules in the liver may be observed on CT [2, 6].

Neurosarcoidosis

Five to 10% of patients with sarcoidosis have clinical recognizable neurological involvement. Usually it presents at onset of the disease associated to other systemic manifestations. It has a predilection for the basal meninges, so cranial nerve involvement, particularly peripheral facial paralysis, sometimes bilateral, are common. Other central nervous system manifestations include aseptic meningitis, seizures, pyramidal tract signs, optic nerve dysfunction, papilledema, hypothalamic and pituitary lesions with diabetes insipidus or hypopituitarism, and cognitive impairment. Spinal cord involvement is rare. Cerebrospinal fluid analysis may show lymphocytosis, increased proteins, and oligoclonal bands. Gadolinium-enhanced magnetic resonance imaging (MRI) may reveal nonenhancing multifocal periventricular and subcortical white matter lesions mimicking those of multiple sclerosis, meningeal enhancement, space-occupying lesions, and hydrocephalus. Peripheral axonal polyneuropathy is not frequent [14].

Musculoskeletal System

Transient or chronic polyarthralgias are common but frank arthritis is not frequent. Asymptomatic muscle involvement is common, but symptomatic diffuse or nodular myopathy is rare. Bone lesions, usually osteolytic, are not frequent and predominate on the hands and foot, but any bone may be affected [2, 6].

Heart

Clinical heart involvement occurs in 5% of patients. Arrhythmias, supraventricular and ventricular, complete heart block, sudden death, papillary muscle dysfunction, and cardiomyopathy with congestive heart failure may be present. Cor pulmonale is usually secondary to chronic pulmonary fibrosis. 24-hour Holter monitoring, Doppler echocardiogram, cardiac PET, and cardiac MRI are useful for the diagnosis. Endomyocardial biopsy may reveal granulomas although the diagnostic yield is low [15].

Other Manifestations

Parotid involvement may produce parotid enlargement and xerostomia. Transient or persistent hypercalcemia, hypercalciuria, rarely with nephrolitiasis and nephrocalcinosis, may be present. Interstitial lymphocytic and granulomatous nephritis and renal failure have been reported. Sarcoidosis of the upper respiratory tract (SURT) may involve any structure, causing more frequently nasal obstruction, crusting, and anosmia. Gastrointestinal, genital, and endocrine glands involvement is rare [2, 6].

Parasarcoidosis

This term includes a group of manifestations that are not caused by granulomatous organ infiltration that may be present with active but also with inactive disease. They may severely affect the quality of life of patients. The most important manifestation is persistent asthenia. Asthenia has been

Table 38.2 Table of signs and symptoms in percentage

	Prevalence (%)	Related signs and symptoms
Intrathoracic (lung, mediastinum) involvement	90	Asymptomatic Dry cough and dyspnea Bronchial hyperreactivity Hemoptysis
Specific (granulomatous) skin lesions	15–25	Maculopapular eruptions Infiltration of old scars and tattoos Subcutaneous nodules Plaques Lupus pernio
Nonspecific	8–40	Erythema nodosum
Eye	15–20	Anterior, intermediate, or posterior uveitis Choroioretinitis Periphlebitis Papilledema, and retinal hemorrhages. Conjunctivitis, lacrimal gland involvement Keratoconjunctivitis sicca
Peripheral lymphadenopathy	10–20	Cervical, supraclavicular, epitroclear, axillary, mesenteric chain, retroperitoneal and inguinal lymph nodes
Spleen	5–10	Splenomegaly Pancytopenia
Liver	20–30	Hepatomegaly Cholestasis Portal hypertension Budd-Chiari syndrome
Nervous system	5–13	Cranial nerve involvement (particularly facial paralysis, sometimes bilateral) Aseptic meningitis, seizures, pyramidal tract signs, optic nerve dysfunction, papilledema, hypothalamic and pituitary lesions with diabetes insipidus or hypopituitarism, and cognitive impairment Spinal cord involvement Peripheral axonal polyneuropathy Small fiber neuropathy with autonomic involvement
Joint	37	Transient or chronic polyarthralgias, periarticular ankle inflammation
Muscle	1	Proximal muscle weakness, myalgia, diffuse or nodular myopathy
Bone	<5	Often asymptomatic; predominate on the hands and foot, also large bones and axial skeleton. More frequently detected since the introduction of ^{18}F-FDG-PET/CT
Heart	5	Arrhythmias, complete heart block, sudden death, papillary muscle dysfunction, and congestive heart failure. Cor pulmonale secondary to chronic pulmonary fibrosis.
Parotid/salivary glands/lacrimal	5–25	Parotid enlargement and xerostomia Lacrimal gland enlargement and/or a dry eyes (sicca) syndrome Heerfordt's syndrome when associated with uveitis, fever, and facial palsy
Renal involvement	0.5–2	Interstitial lymphocytic and granulomatous nephritis, chronic renal failure, and proteinuria
Hypercalcemia/ hypercalciuria	5–10	Transient or persistent hypercalcemia, hypercalciuria, nephrocalcinosis, and nephrolithiasis.
SURT	0.5–6	Nasal stuffiness, nasal bleeding, crusting, anosmia
Gastrointestinal tract	1	Abdominal pain, hematemesis, blood per rectum
Genitourinary tract	0.3	Breast and vulva mass

reported as the most frequent symptom of sarcoidosis. It is important to exclude organic involvements, such as respiratory failure, obstructive sleep apnea, anemia, and hypothyroidism. Small fiber neuropathy with autonomic involvement, depression, and cognitive dysfunction have also been reported [16].

Table 38.2 provides a list of signs and symptoms according to the involved organs.

Ancillary Tests

In addition to the alterations according to the organs involved, lymphopenia, mild eosinophilia, and hypergammaglobulinemia may be observed. At diagnosis, at least 60% of patients have increased serum angiotensin-converting enzyme (SACE) level, although it is not specific. Pulmonary function tests (PFT) may reveal decreased forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLco). Bronchial obstruction with decreased forced expiratory volume in 1 s (FEV1) may be present as a consequence of peripheral airway involvement, endobronchial inflammation, bronchial hyperreactivity, and advanced pulmonary fibrosis with irreversible airways distortion. Six minutes walking test should be performed in patients with a decrease in DLco. Its decrease may suggest the presence of pulmonary hypertension. Thoracic high-resolution computed tomography (HRCT) may be useful in patients with atypical radiological findings, to detect areas of active alveolitis in cases with pulmonary fibrosis, and to detect specific complications in the lung. In addition to the BHL, the most common findings are widespread small nodules with a bronchovascular and subpleural distribution, miliary pattern, thickened interlobular septae, ground-glass areas, and confluent nodular opacities with air bronchograms, with predilection for mid and upper lung zones. With advanced fibrosis, architectural distortion, hilar retraction, fibrous bands, bronchiectasis, and bullae may be observed. The demonstration on bronchoalveolar lavage (BAL) of a lymphocitic alveolitis with a proportion of CD4/CD8 > 3.5 has a sensitivity of 53% and a specificity of 94%. However, BAL is not routinely performed unless a transbronchial lung biopsy (TLB) or cryobiopsy is indicated [9–11]. ^{18}Fluor-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET/CT) may be useful for complex cases with diagnostic difficulties to detect the presence of hidden granulomatous focus of activity and to identify areas for biopsy. ^{18}F-FDG-PET/CT may be also useful in cases of advanced pulmonary fibrosis to differentiate active involvement, still susceptible to be treated, vs. fibrotic lesions that will not improve with immunosuppressive treatment [1]. Tuberculin skin test is negative in more than 80% of patients. However, Interferon-gamma release assays (IGRAs) (Quantiferon®) for the detection of tuberculosis is currently recommended.

Diagnostic Criteria

The diagnosis of sarcoidosis is based on a compatible clinical and radiological picture, demonstration of noncaseating granulomas with negative cultures for mycobacteria and fungus, and exclusion of other granulomatous diseases [2, 17, 18]. Figure 38.1 provides an algorithm for the diagnostic assessment of sarcoidosis.

The type of biopsy will depend on the involved organ and its accessibility. In the case of mediastinal involvement, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) of enlarged intrathoracic lymph nodes has a diagnostic yield of 87% and is less invasive than mediastinoscopy, although this has a diagnostic yield of 98%. TLB has a diagnostic yield of 40-90%. It is recommended that four to five lung biopsies be performed. TLB is more probable to be diagnostic in patients with parenchyma

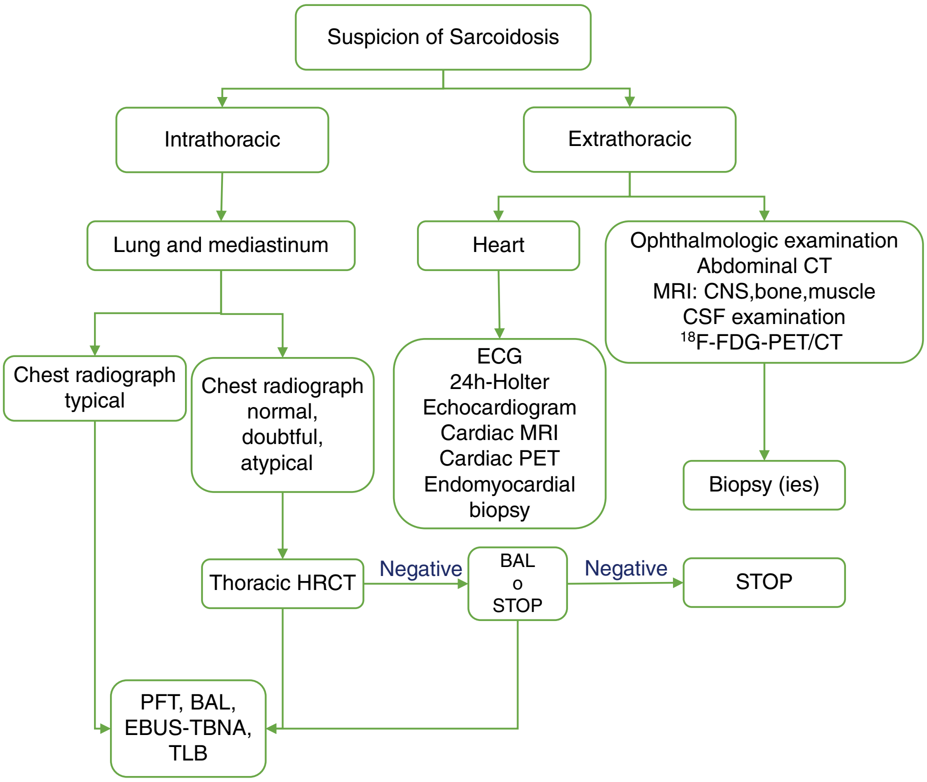
Suspicion of Sarcoidosis
Intrathoracic
Extrathoracic
Lung and mediastinum
Heart
Ophthalmologic examination
Abdominal CT
MRI: CNS,bone,muscle
CSF examination
^{18}F-FDG-PET/CT
Chest radiograph typical
Chest radiograph normal, doubtful, atypical
ECG
24h-Holter
Echocardiogram
Cardiac MRI
Cardiac PET
Endomyocardial biopsy
Biopsy (ies)
Thoracic HRCT
Negative
BAL o STOP
Negative
STOP
PFT, BAL, EBUS-TBNA, TLB

Fig. 38.1 Algorithm for the diagnostic assessment of sarcoidosis

involvement (radiological stage II or III) than in those with a normal lung parenchyma (radiological stage 0 or I). Skin and peripheral lymph node biopsies have a high yield. Less frequently, biopsies of liver, lacrimal and parotid glands, conjunctiva, muscle, upper respiratory tract (nasal mucosa), scalene lymph node (Daniel's biopsy), nervous system, spleen, bone, heart, and kidney may be used as well. When available, the Kveim-Siltzbach test has a sensitivity of 70–90% and a specificity of 97%. Occasionally, granulomatous cells may be seen in cytological specimens obtained by fine needle aspiration of mass lesions in patients with suspected sarcoidosis. This may be useful in excluding malignancy, and may support the diagnosis, although it is not an absolute proof. Importantly, a biopsy with the typical noncaseating granulomas is nonspecific for sarcoidosis and requires a differential diagnosis with other granulomatous diseases that varies according to every organ [18]. Infectious diseases, particularly tuberculosis, and tumor-related sarcoid reactions should always be excluded. When the clinical and radiological findings are not typical for sarcoidosis, it is recommended to obtain at least two positive biopsies in different organs. However, 15–20% of biopsies with granulomas remain without a specific etiology. This has been named as granulomatous lesions of unknown significance (GLUS syndrome) although some authors consider them as mono-organ sarcoidosis [2]. On the other hand, some clinical and radiological pictures, such as Löfgren's syndrome and Heerfordt's syndrome, are so typical of sarcoidosis, that histological confirmation may not be necessary [2]. Asymptomatic BHL is highly suggestive of sarcoidosis and, according to some authors, a biopsy confirmation may not be necessary. However, an EBUS-TBNA is currently recommended [5]. Once the diagnosis has been established, the workup for patients with sarcoidosis includes an assessment of the extension and severity of organ involvement, an evaluation to see whether the disease is stable or progressing, and so determine if therapy is indicated or it requires a follow-up without treatment.

Prognosis and Therapy

In asymptomatic patients and those with an acute presentation, the disease usually resolves spontaneously without treatment. LS has an excellent prognosis. Rest, nonsteroidal anti-inflammatory drugs, or a short course of low-dose prednisone are useful to treat erythema nodosum. In other cases, the disease persists active for years, with a tendency to wax and wane, but with minimal organ damage and no significant clinical repercussion. In these cases, treatment is usually not indicated. Ten to 30% of patients follow a chronic and progressive course for more than 5 years in spite of therapy [8]. Occasionally, recurrence of sarcoidosis many years after spontaneous remission may occur, particularly in patients with Löfgren's syndrome. Pregnancy is not contraindicated except in severe chronic disease. However, it may be relapse after parturition. Mortality is less than 5% [8].

Corticosteroids are the therapy of choice. However, there is a controversy about when to treat a patient with sarcoidosis. Although corticosteroids suppress the inflammatory process, it has not been demonstrated that they alter the long-term outcome of the disease. In consequence, the objective of treatment must be the symptomatic control and prevention of irreversible organ damage, particularly in major organs, such as lung, eye, heart, and CNS, trying to cause the minimum secondary effects. Alternate-day therapy may be used. Relapses a few months after the suppression of treatment may occur [19].

Pulmonary Sarcoidosis

In chest radiograph stages, II and III treatment should be administered in presence of symptoms, radiological progression, or decreased lung function. In asymptomatic patients with normal lung function, a period of 6–12 months observation is indicated, and treatment should be administered if the patient becomes symptomatic, or there is persistence or progression of radiological findings, or lung function deteriorates. In stage IV, fibrosis may coexist with active alveolitis, and treatment is recommended with a re-assessment of symptoms and lung function 3 to 6 months later. The recommended therapy is prednisone, 20–30 mg/day, with slow tapering, at least for 1 year. The best way to assess the treatment efficacy in pulmonary sarcoidosis is periodical evaluation of symptoms, chest radiograph, and lung function. Inhaled corticosteroids may be useful if associated bronchial hyperreactivity is present [10, 11, 19].

Extrapulmonary Sarcoidosis

The main indications for treatment are posterior uveitis, neurosarcoidosis, cardiac involvement, and persistent hypercalcemia. Severe cutaneous lesions, hypersplenism, and severe liver, upper respiratory tract, and kidney involvement may also require treatment. The recommended therapy is prednisone, 30–40 mg/day, with slow tapering, at least for 2 years. However, some patients may need more prolonged treatment [19]. Severe neurosarcoidosis and severe cardiac sarcoidosis, may be treated initially with high-dose methylprednisolone intravenous pulse therapy. Anterior ocular involvement is treated with topical corticosteroids.

Table 38.3 Most common drugs for the treatment of sarcoidosis

First-line treatment		
	Usual dose	Main side effects
Glucocorticoids	Prednisone 20–30 mg/day for pulmonary sarcoidosis in a tapering schedule ≤40 mg/day for extrapulmonary sarcoidosis in a tapering schedule Maintenance dose <10 mg/day In life-threatening situations (severe neurosarcoidosis and severe cardiac sarcoidosis) intravenous methylprednisolone, 500–1000 mg daily for 3 days, and then once a week for 8 weeks followed by prednisone 20 mg/day in a tapering schedule	Weight gain, stretch marks, diabetes, infections, hydrosaline retention, muscle weakness, glaucoma, cataracts, insomnia, personality changes, osteoporosis and osteonecrosis of the femoral head
Second-line treatment		
	Usual dose	Main side effects
Methotrexate	10–20 mg once per week orally or subcutaneous Folic acid supplementation weekly	Gastrointestinal effects, liver toxicity, hematological toxicity
Azathioprine	50–200 mg/day	Gastrointestinal effects, leucopoenia, hepatotoxicity, pancreatitis, lymphoproliferative syndromes and nonmelanoma skin cancer.
Hydroxychloroquine	400 mg/day for 2 weeks followed by 200 mg/day	Ocular toxicity (corneal and retinal)
Third-line treatment		
	Usual dose	Main side effects
Infliximab	3–5 mg/kg in weeks 0, 2, 6, and every 4–8 weeks intravenously	Allergic reactions, increased risk of infection (tuberculosis), increased risk of some cancers, development of anti-infliximab antibodies
Adalimumab	40 mg subcutaneously every 2 weeks	Risk of infection (tuberculosis)

Refractory Sarcoidosis

Some cases of sarcoidosis may be refractory to corticosteroid treatment. If the dose of prednisone needed to keep the disease under control is superior to 10 mg/day for a prolonged time, various second-line medications may act as steroid-sparing agents. They are usually administered combined with low-dose prednisone. The most used are methotrexate and hydroxychloroquine. Other drugs reported to be useful in uncontrolled reports include azathioprine, cyclophosphamide, pentoxifylline, tetracyclines, and mycophenolate mofetil. A third line with biological drugs, such as infliximab, has been useful for some severe forms of neurosarcoidosis, cardiac sarcoidosis, or deforming cutaneous lesions. Adalimumab is useful in refractory posterior uveitis [19]. Table 38.3 shows a summary of the most frequently used drugs for the treatment of sarcoidosis. Pacemaker and automatic implantable cardioverter defibrillator may be necessary in cardiac sarcoidosis. Lung and other organ transplantation have been successfully performed for end-stage disease.

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Spondyloarthritis

39

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Abstract

Spondyloarthritis (SpA) represents a collection of prevalent inflammatory rheumatic disorders characterized by arthritis affecting the spine or peripheral joints. They often present with additional features like enthesitis, dactylitis, and potential extra-articular symptoms such as uveitis and skin rashes. While these conditions within the SpA group share a common genetic predisposition such the human leukocyte antigen (HLA) B27 gene, the strength of this association varies significantly among different SpA subtypes and diverse ethnic populations. Additionally, environmental factors play a crucial role in triggering these diseases in genetically susceptible individuals. Radiographically, sacroiliitis is a distinctive hallmark of this group of disorders and can be instrumental in making a diagnosis when present. Over the years, various diagnostic and classification criteria have been developed. The Assessment of SpondyloArthritis international Society (ASAS) international working group has developed criteria that enable the identification of SpA before structural changes become evident in the spine. Furthermore, magnetic resonance imaging (MRI) changes have been incorporated into the new classification criteria for early axial SpA and are now recognized as a major diagnostic tool. Until recently, there were no disease-modifying antirheumatic drugs who inhibit disease progression. However, in the past decade, extensive research has focused on tumor necrosis factor (TNF)-alpha blocking agents and various other biologics, which have become the primary mode of therapy to offer patients an effective treatment option.

Keywords

Spondyloarthritis · Spondyloarthropathy · Ankylosing spondylitis · Psoriatic spondylitis · Reactive arthritis · Inflammatory · Bowel · Disease · Spondylitis

Introduction

Spondyloarthritis is a group of diverse interrelated inflammatory arthritides, which share multiple clinical features as well as common genetic predisposing factors [1]. The group includes the prototypical disease ankylosing spondylitis (AS), reactive arthritis (ReA) or spondyloarthritis, psoriatic arthritis (PsA) or spondyloarthritis, SpA associated with inflammatory bowel disease (IBD) (Crohn's disease or ulcerative colitis), undifferentiated SpA (uSpA) [1], and juvenile-onset spondyloarthritis.

Spondyloarthritides are characterized by sacroiliitis with inflammatory back pain, peripheral arthropathy, absence of rheumatoid factor and subcutaneous nodules, enthesitis, extra-articular or extra-spinal involvement, including the eye, heart, lung, and skin. There is a tendency towards familial aggregation as well as varying association with HLA-B27, depending on the population studied; however, at least six other genes associated with AS have been discovered. The similarities in clinical manifestations and the genetic predisposition suggest that these disorders share some pathogenic mechanisms. SpA has large variation in reported prevalence: from 0.2% in Southeast Asia to 1.61% in Northern

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Arctic Communities [2], while the overall prevalence of SpA is like that of rheumatoid arthritis. Several sets of classification criteria have been developed with significant overlaps.

Signs and Symptoms

Ankylosing spondylitis is the most common and most typical form of SpA, with a prevalence of 0.2–1.2% in the Caucasian population, depending on regional genetic and environmental factors. This prevalence tends to be higher in populations with a higher prevalence of HLA-B27 positivity. Historically, AS was considered to affect men up to ten times more commonly than women; however, recent epidemiological studies demonstrated a lower male to female ratio, approximated at 3:1 [3]. The initial symptoms, typically in the early adulthood, are usually of dull pain over the buttock and lower lumbar area, accompanied by morning stiffness, relived with exercise, and worsened with inactivity. This inflammatory back pain, which usually responds well to NSAIDs, may be unilateral or bilateral and may alternate from side to side. Since low back pain is very common in the general population, the diagnosis of AS is usually delayed by years. Until recently, it was commonly believed that the median time of delay from the onset of symptoms to AS diagnosis ranged from 5 to 11 years. However, in individuals with a positive HLA-B27 gene, the condition typically initiates up to 5 years sooner compared to those who were negative for HLA-B27 AS [4]. However, recent literature indicated an updated diagnostic delay time of 2 years, shorter than previously reported and the newly Assessment of SpondyloArthritis international Society (ASAS) diagnostic criteria, described below, are thought to contribute to these findings. Other initial features include localized pain as a sign of enthesitis, inflammation at bone insertion sites of ligaments and tendons. The pain expressed due to the enthesopathy depends on the affected location (heels, ischial tuberosities, costosternal junctions, greater trochanters, and other locations). Frank arthritis may occur in 25–35% of the patients, usually involving large joints in an asymmetrical fashion (shoulder, knee, ankle, and hip). Involvement of the cervical spine with neck pain leading to a reduced range of motion is generally a later manifestation in the course of the disease. Dactylitis, inflammation of an entire digit, commonly termed “sausage digit,” is another typical feature of the SpA, mainly in PsA and ReA. It is thought to arise from joint and tenosynovial inflammation. Other clinical features include recurrent acute anterior uveitis, which occurs in about 30% of the patients and can antedate the spondylitis, cardiovascular manifestations (aortic insufficiency, congestive heart failure, aortitis, angina, pericarditis, and cardiac conduction abnormalities). Dyspnea, cough, or hemoptysis can result from upper lobe pulmonary fibrosis.

Psoriatic arthritis (PsA) is present in one of four psoriasis patients. Several patterns of joint involvement have been described: arthritis mutilans, peripheral oligoarthritis or polyarthritis, spondylitis, and distal interphalangeal joint arthritis (fingers and toes), which are commonly affected (>50%). Cervical spine disease is common (>50%) and usually progresses in severity in parallel with the peripheral joint disease. Psoriasis of the nails (in 83%) or skin may precede or follow joint involvement. The typical psoriatic lesions may be hidden in the scalp, behind the ears, gluteal folds, or umbilicus, occasionally even unnoticed by the patient. Extra-articular features include constitutional symptoms, fatigue, and iritis or uveitis. Similarly, to other SpAs, various biomarkers have been suggested for assessing psoriatic arthritis. Of these biomarkers, which are still being studied, CRP, matrix metalloproteinase-3, osteoprotegerin (OPG), and other cartilage biomarkers are thought to be promising. PsA, like other SpAs, is associated with HLA-B27, predominantly in those patients who suffer from axial involvement such as sacroiliitis or spondylitis.

Reactive arthritis usually manifests itself as arthritis, 2–4 weeks following a urogenital or enteric infection, often in patients bearing the HLA-B27 antigen. The risk of developing ReA has been shown to occur up to 50 times higher in an HLA-B27 positive individual, as opposed to a B27-negative patient, following exposure to a preceding infection. Furthermore, HLA-B27 positivity is thought to be involved with a more severe disease and tends to progress into a more chronic form of the disease. Enthesitis, the typical feature of ReA, is occurring in 70% of the patients, usually manifesting itself as a calcaneal spur with heel pain or Achilles tendinitis. The knees may be involved with large effusions. Sacro-ileitis and inflammatory back pain with spondylitis may occur in almost 50% of the patients. Dactylitis of the fingers or toes is also typical for ReA. A wide range of extra-articular features of ReA include urethritis, cervicitis, vulvovaginitis, salpingitis, and prostatitis. There are also typical dermatological manifestations, oral ulcers, erythema nodosum, conjunctivitis, as well as cardiac involvement.

IBD (enteropathic) associated arthritis is usually a peripheral large joint, lower limb asymmetric oligoarthritis. It accompanies IBD in about 10% of patients and occasionally antedates it. Occasionally, symmetrical small-joint polyarthritis may also occur in this group of patients. As with the other SpA, extra-articular and extra-intestinal features, such as uveitis, erythema nodosum, pyoderma gangrenosum and others, are more common in Crohn’s disease than in ulcerative colitis and occur more often in patients with arthritis. The synovitis usually runs in parallel with the bowel disease and may resolve completely following colectomy. The spondyloarthritis and sacroiliitis run however an independent course compared to the bowel disease, and usually run a milder course compared to AS. HLA-B27 association in IBD-associated arthritis is weaker than in AS, and only around 40% of the patients are found to be positive for B27.

Undifferentiated spondyloarthropathy or spondyloarthritis (uSpA) is used to describe manifestations of SpA in patients who do not meet criteria for any of the well-defined spondyloarthritis. There is a female predominance of 2:1, and the clinical manifestations of this type of SpA are basically like all other SpAs with fewer extra-articular manifestations. Like AS, uSpA is also linked to HLA-B27 and other HLA alleles, suggesting that this subgroup of SpAs is also genetically determined. Long-term follow up of these patients shows that even after years of active disease, sacroiliitis and spondylitis are either absent or appear very mildly on routine radiographs. Prognosis is generally good.

Juvenile-onset spondyloarthropathy is an asymmetric, mostly lower extremity peripheral arthritis, in a similar manner to adult AS, that begins most commonly in boys aged 5–16. Enthesitis and dactylitis are prominent features of the disease in children. MRI allows discovery of sacroiliac joint involvement at a much earlier time point than do radiographs. Systemic manifestations are more frequent in the juvenile SpA than in the adult form.

Laboratory Findings and Serological Markers

There are no specific laboratory tests for the SpAs. The diagnosis is therefore made by combining clinical criteria with radiological findings. Inflammatory disease markers, such as CRP, serum amyloid A (SAA), and erythrocyte sedimentation rate (ESR), are generally elevated, though not in all patients, and are therefore less useful for monitoring disease activity of AS. However, CRP, SAA, and interleukin-6 are historically and currently considered the best predictors of treatment response while an elevated level of CRP was found to be a strong positive predictor of sacroiliitis progression. Additional biomarkers have been suggested as new candidates to represent disease activity in SpA, including the soluble cytotoxic T lymphocyte-associated molecule-4 (CTLA-4) and synovial CD163+ macrophages, both are thought to be associated with T cell regulation and global inflammation.

The Assessment of SpondyloArthritis international Society (ASAS) international working group has adopted and validated the Ankylosing Spondylitis Disease Activity Score (ASDAS), an instrument for assessing disease activity in ankylosing spondylitis. ASDAS components including patient-reported outcomes, such as back pain, duration of morning stiffness, patient global assessment, peripheral joint complaints, and CRP measurement [5]. Disease activity scores are essential to measure treatment responses, as well as to decide whether patients might be candidates for treatment with the modern biologic drugs. A mild normocytic anemia and thrombocytosis may be present in the more severe cases. Rheumatoid factor and antinuclear antibodies are generally absent in the SpAs. Radiographic changes of the sacroiliac joints are usually symmetric and consist of blurring of the subchondral bone plate, followed by erosions and sclerosis of the adjacent bone. Conventional plain radiographs of the pelvis serve as a good screening tool for evaluation of the sacroiliac joints in patients with inflammatory back pain. Nuclear scanning, computed tomography (CT), or magnetic resonance imaging (MRI) may be employed if the plain X-rays of the pelvis are negative or equivocal. Positive MRI findings have the same significance as a positive test for HLA-B27. It should be noted that based on recent data from the ASAS group, MRI changes have been included for the first time in the new classification criteria of early axial SpA and are now considered as a major tool in the diagnosis, allowing the diagnosis of early forms of the disease long before structural damage becomes visible on X-rays [6]. The presence of subchondral bone marrow edema on the STIR sequence or signs of osteitis on the T1-weighted gadolinium augmented sequence are positive; however, nonspecific radiological signs indicate the presence of sacroiliitis. Nevertheless, MRI also allows visualization of synovial fluid and synovitis within the sacroiliac joint.

Pathogenesis and Environmental Aspects

The exact etiology and pathogenesis of the SpAs remains unclear, though strong evidence supports the genetic background to play a major role in the susceptibility of this group of diseases, together with environmental factors, which seem to trigger the genetically predisposed patients, leading to the release of pro-inflammatory cytokines. The first and most frequently documented genetic factor identified was the tissue antigen HLA-B27, a major histocompatibility complex (MHC), which is present in up to 90% patients in most of the ethnic groups that present with the disease. However, some of these subtypes are sufficiently prevalent, so that the relative strength of their association with AS is unclear. Other than B-27, MHC variants who are known to be associated with AS are HLA-B40, HLA-B51, HLA-B7, HLA-A2, and HLA-DPB1 [7]. Regarding HLA-B27 specifically, it exhibits significant genetic polymorphism, comprising up to 105 known subtypes which are encoded by 132 alleles. Interestingly, decreasing north-south gradient in the general frequency of HLA-B27 has been noted.

In the general population, AS is likely to develop in up to 6% of HLA-B27-positive adults. Approximately 4–8% of the healthy population is positive for HLA-B27. Family studies have shown that first-, second-, and third-degree relatives of patients with AS have a significantly increased risk of developing AS (relative risks of 94, 25, and 3.5, respectively). 60% of psoriatic patients with spondylitis and IBD-associated spondylitis are positive for B27, whereas 60–80% of ReA patients and 20-25% of patients with undifferentiated SpA are positive for B27. HLA typing for B27, should however not be used as a routine diagnostic test, and should be only reserved for rare clinical situations in which the presentation is atypical or complex.

Association of AS with the MHC explains less than half of the familiarity of AS. Major advances have occurred in recent years in demonstrating non-MHC genes involved. These include genes involved in peptide editing for loading onto class I MHC molecules (ERAP1 gene, formerly known as the ARTS-1 gene), as well as cytokine genes such as interleukin 1A (IL-1A) and those involved in the Th17 network (IL-23R gene), previously known to be associated with inflammatory bowel disease and psoriasis. According to present studies, the onset of AS is thought to result from aberrant peptide presentation to CD8+ and CD4 T cells, misfolded HLA-B27 molecules, HLA-B27 dimers or beta-2 m accumulation and deposition. Furthermore, aberrant recognition by specific immunoreceptors may occur in several pathways, which may be subsequently contributing to downstream cytokine dysregulation, particularly in the IL-23/IL-17 axis.

Except for bacteria which clearly trigger ReA, this clear association has not been substantiated in any of the other SpA though it has been shown already over a decade ago that some forms of SpA may be triggered by enterobacterial infections, and certain subtypes share sequence homologies with these bacterial antigens, such as *Klebsiella pneumoniae* nitrogenase [8]. The true significance of this molecular mimicry theory remains unclear and remains debatable. However, the importance of intestinal pathogens was further illustrated by the HLA-B27 transgenic rat model, in which arthritis and colitis did not develop in germ-free conditions. Subclinical gut inflammation has been shown to occur in patients with ankylosing spondylitis as well as with other SpAs, although there is no obvious link to explain this association between the joint and the gut inflammation. In the case of ReA, there is a clear association with a previous infection, either intestinal or genitor-urinary, triggering HLA-B27-associated ReA. These patients develop a chronic SpA following infections with *Yersinia enterocolitica*, *Salmonella typhimuriuim* and enteritides, *Shigella flexneri, Chlamydia trachomatis, Ureaplasma urealyticum*, and *Campylobacter jejuni*. Other pathogenic organisms have been implicated in ReA, however, with less frequent associations. DNA from some of the more frequent organisms has been found by PCR in synovial cells and fluid of patients with ReA. This finding of bacterial products in the joints provides a potential link between enteric infection and joint inflammation.

Worldwide Incidence and Prevalence

Many studies have attempted to assess the estimates of the incidence and prevalence of AS and SpAs in various populations using different methods. Examining hospital records spanning 50 years in Rochester, USA, it was observed that the annual incidence of AS was approximately 1 case per 10,000 males and one-third of that rate in females [9]. Likewise, in the case of non-radiographic axial SpA, it is currently believed that there is an even distribution between the sexes. These patterns were also identified in a 10-year study conducted in both Norwegian and Finnish populations [10]. Consequently, these nearly identical findings point to the consistent epidemiological characteristics of Ankylosing Spondylitis (AS) in these countries. However, in countries like Japan or Greece, the incidence, as well as the prevalence of AS, was found to be much lower, as opposed to a much higher incidence in the Arctic regions [11]. AS is rare in Africa though when it does occur it is still associated with HLA-B27.

The prevalence of ankylosing spondylitis (AS) closely mirrors the distribution of HLA-B27 in various populations, exhibiting global variations that span a diverse range of ethnic backgrounds and geographic regions [7]. For instance, in populations of European descent, HLA-B27 is found in approximately 8% of individuals, while AS affects roughly 0.5% of this group [2]. Conversely, in populations with a lower prevalence of HLA-B27, such as African Americans, the occurrence of AS is less frequent. Studies conducted in the United States, Germany, and Lithuania have indicated that SpA ranks among the most common rheumatic diseases, possibly rivaling the prevalence of rheumatoid arthritis [12].

While prevalence rates for PsA and ReA have not been extensively investigated, the pooled prevalence of all spondyloarthritis types, including peripheral forms, varies from 0.2% in southeast Asia to as high as 1.61% in Northern Arctic communities [2]. In surveys conducted across different regions, the reported prevalence of axial spondyloarthritis falls within a range of 0.32–1.4% [13].

Diagnostic Criteria

In 2009, the Assessment of SpondyloArthritis international Society (ASAS) introduced diagnostic criteria for axial spondyloarthritis [14], and in 2011, they established criteria for peripheral spondyloarthritis [15]. These criteria are designed to distinguish between patients primarily experiencing axial symptoms and those with predominantly peripheral manifestations. They consider magnetic resonance imaging (MRI) findings and HLA-B27 testing. However, recognizing the complexity of spondyloarthritis, where both

Table 39.1 ASAS Classification Criteria for Axial Spondyloarthritis (SpA)[b]

(a) In patients with 3 months or more, of back pain and age of onset <45

Sacroiliitis on imaging[a] plus 1 or more SpA feature **OR HLA-B27** plus 2 or more other SpA features

SpA features:

- Inflammatory back pain (IBP)
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's/colitis
- Good response to NSAIDs
- Family history of SpAHLA-B27
- Elevated CRP

(b) In patients with peripheral symptoms ONLY

Arthritis or enthesitis or dactylitis plus

1 or more SpA feature

- Uveitis
- Psoriasis
- Crohn's/colitis
- Preceding infection
- HLA-B27
- Sacroiliitis on imaging

OR

2 or more other SpA features

- Arthritis
- Enthesitis
- Dactylitis
- IBP ever
- Family history for SpA

[a] Sacroiliitis on imaging: Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA **OR** definite radiographic sacroiliitis according to the modified New York criteria

[b] Reproduced with permission from the Assessment of SpondyloArthritis International Society (ASAS) Slide Library 2009; (http://www.asas-group.org/)

axial and peripheral symptoms can coexist, the ASAS also developed criteria for patients presenting with a combination of axial and peripheral spondyloarthritis [15].

These criteria, presented in Table 39.1a, b[b], offer a flexible approach to diagnosing SpA, as they enable the diagnosis of SpA without relying on imaging, in cases when a patient tests positive for HLA-B27 and exhibits two other characteristic features of SpA. Moreover, they provide the opportunity for earlier diagnosis by considering MRI evidence of sacroiliitis, rather than waiting for the development of typical radiographic changes. Another advantage of these criteria, when compared to earlier sets, is their ability to readily classify patients with undifferentiated SpA based on their primary symptoms. This not only streamlines the diagnostic process but also enhances the accuracy of classification. The ASAS criteria demonstrate a sensitivity of 79.5% and a specificity of 83.3%, further highlighting their effectiveness [15].

Until a few years ago, PsA lacked clearly defined classification criteria. A global effort was made to address this gap, resulting in the creation of the Classification Criteria for Psoriatic Arthritis (CASPAR) [16]. This group suggested the following criteria for the diagnosis and classification of PsA, providing sensitivity of 91.4% and specificity of 98.7%.

- Presence of musculoskeletal inflammation (inflammatory arthritis, enthesitis, or inflammatory back pain).
- **PLUS 3** points from the following:
- Skin psoriasis (present) (**2** points), previously present by history (**1** point), or a family history of psoriasis (**1** point) if the patient is not affected.
- Nail lesions (onycholysis, pitting) (**1** point).
- Dactylitis (present or past, documented by a rheumatologist)—**1** point.
- Negative rheumatoid factor—**1** point.
- Juxtaarticular bone formation on radiographs (distinct from osteophytes) –.
- **1** point.

Moreover, various screening tools have emerged to enhance the identification of this condition by family physicians, dermatologists, and rheumatologists. A significant number of these screening tools exhibit moderate to high levels of sensitivity and specificity.

Prognosis

Spondyloarthritis exhibits a distinctive pattern marked by recurrent episodes of mild to moderate inflammation, alternating with periods of reduced or no inflammation. Early diagnosis and intervention play a pivotal role in preventing structural damage and disability. Nevertheless, effective treatment often enables most patients to lead productive lives with minimal or no disability, even in the presence of occasional back stiffness.

However, a small subset of individuals may experience chronic progressive disease, leading to incapacitating conditions like spinal fusion, particularly with thoracic kyphosis, or erosive disorders impacting peripheral joints, notably the hips and shoulders. It remains unclear why certain individuals respond better than others, though hip involvement and early-onset cervical spine disease seem to play a role. Uveitis often signifies a more severe disease course, while predictors of poor prognosis encompass features like peripheral joint involvement, early disease onset, elevated erythrocyte sedimentation rate (ESR), and poor response to nonsteroidal NSAIDs.

Several studies offered predictive factors to identify potential candidates for antitumor necrosis factor-α treatment among AS patients. These predictors, including age, the Bath AS Functional Index (BASFI score), enthesitis, therapy, C-reactive protein (CRP), and HLA-B27 status, can serve as valuable guidance for clinicians in their treatment decisions.

In AS, patients with long-standing and severe disease, as well as those with substantial extra-articular manifestations, face an increased risk of mortality. Factors such as the duration and intensity of inflammation, alongside circulatory and cardiovascular issues, contribute to this elevated risk. Similarly, PsA often accompanies comorbidities like obesity, diabetes, hyperlipidemia, and hypertension, and it is associated with accelerated atherosclerosis, resulting in higher cardiovascular morbidity and mortality. The underlying causes of increased cardiovascular mortality appear to be multifactorial, arising from both prolonged inflammation and a high prevalence of conventional cardiovascular risk factors. Consequently, a dual approach is imperative for enhancing long-term survival: early diagnosis and aggressive anti-inflammatory treatment, coupled with a vigilant strategy addressing cardiovascular risk factors.

Prevention

As genetic factors seem to contribute to AS and other SpAs, it is challenging to prevent these conditions outright. Nonetheless, understanding one's personal risk factors can aid in the early identification and treatment of the disease. Individuals who possess the HLA-B27 gene and have a family history of AS face approximately a 20% risk of developing the condition, particularly if they are under the age of 40. For those older than 40, the likelihood of AS occurrence is significantly reduced. Failing to recognize SpA and subsequently administer effective treatments can lead to a significant portion of individuals developing severe spinal limitations, resulting in substantial morbidity, decreased quality of life, and even increased mortality. Hence, timely and appropriate treatment not only alleviates joint discomfort but also helps stave off or delay the onset of physical deformities.

Treatment of Spondyloarthritides

The current international management guidelines, specifically the ASAS/EULAR[1] [17] and ACR/SAA/SPARTAN[2] [18] recommendations, offer a cohesive approach for conditions such as axial spondyloarthritis, psoriatic arthritis, and peripheral spondyloarthritis. These guidelines were initially established in 2014 by a multinational task force and are continuously being updated. The primary therapeutic objective is the attainment of remission, with the achievement of low disease activity considered a secondary goal. In both radiographic and non-radiographic forms of axial spondyloarthritis, remission is defined as having a low Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score coupled with normal CRP values or a low Ankylosing Spondylitis Disease Activity (ASDAS) score, which incorporates measurements of CRP or ESR [19].

Nonsteroidal anti-inflammatory drugs (NSAIDs), when administered at their full anti-inflammatory dosages and complemented by physical therapy, have traditionally represented the cornerstone of treatment for individuals with spondyloarthritis. These treatments primarily focus on mitigating symptoms, as NSAIDs have been demonstrated to have remarkable efficacy in alleviating back pain and stiffness. The use of NSAIDs should be used according to the specific symptoms, clinical signs, disease activity, severity, and functional status of each patient.

Conventional disease-modifying antirheumatic drugs (DMARDs) like methotrexate (MTX), sulfasalazine (SZA), or leflunomide are generally ineffective in addressing the axial manifestations of spondyloarthritis. However, they may have a limited role in managing peripheral manifestations when they coexist with axial disease. A debated topic revolves around the coadministration of a conventional DMARD with a biologic medication could potentially prevent the development of anti-drug antibodies (ADAs), thus enhancing its effectiveness and longevity. As contradictory findings exist many trials, this combined approach is not presently recommended.

Systemic corticosteroids have limited efficacy in managing the inflammatory processes associated with spinal and axial conditions, in contrast to their benefits in other inflammatory arthritic conditions. Bisphosphonates, on the other hand, may yield a slight positive impact on both the underlying osteoporosis and the inflammatory disease, contributing specifically to spinal symptoms.

The management of extra-articular manifestations in spondyloarthritis should be determined according to specific clinical context. While some patients may require total hip arthroplasty, the performance of spinal osteotomy is a rarely pursued treatment option.

Five TNF inhibitors are available in Europe, the USA, and other regions worldwide, for the treatment of AS: infliximab, etanercept, adalimumab, golimumab, and certolizumab [7]. The administration of any of these medications leads to notable improvements in various aspects of AS, including joint-related symptoms, CRP levels, and MRI-detectable inflammation in the sacroiliac joints, especially in active AS patients for whom conventional NSAID treatment has proven ineffective. Early intervention with these drugs may also result in achieving remission without the need for ongoing medication. The effectiveness of TNF inhibitor drugs can vary in the management of certain comorbid conditions like IBD and uveitis. Indicators of a more favorable response to TNF blockers in axial spondyloarthritis include elevated CRP levels, a shorter duration of symptoms (or younger age), and the presence of active MRI-detected inflammation. Multiple large-scale, randomized, placebo-controlled trials have investigated the use of four of the available TNF inhibitors in both AS and psoriatic arthritis, demonstrated good short-term and long-term improvements in clinical and radiological parameters. As per the ASAS recommendations, TNF antagonists appear to be a safe and effective option for the long-term treatment of patients with spondyloarthritis. However, it is currently suggested that TNF inhibitors be considered for patients with peripheral arthritis unresponsive to conventional therapy and enduring persistently high disease activity, or for those with isolated spinal involvement. This cautious approach is due to the ongoing need to evaluate their long-term safety and their potential to prevent structural damage through prospective randomized controlled trials. It has also been shown that survival of TNF antagonists in SpA is better than in rheumatoid arthritis.

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[1] ***ASAS*** *- Spondyloarthritis International Society,* ***EULAR*** *- The European Alliance of Associations for Rheumatology*

[2] ***ACR*** *- American College of Rheumatology,* ***SAA*** *- Spondylitis Association of America,* ***SPARTAN*** *- Spondyloarthritis Research and Treatment Network*

Anakinra, an interleukin-1 receptor antagonist, and abatacept, a T cell modulator, were tested in small prospective open-label trials for ankylosing spondylitis but did not surpass expected placebo responses. Similarly, a study tested rituximab, a monoclonal antibody targeting CD20 on B cells, yielded inconclusive results. Tocilizumab and sarilumab, both monoclonal antibodies directed against the IL-6 receptor, were tested in two placebo-controlled double-blind studies for anti-TNF-naive patients with active AS and showed no significant efficacy. In contrast, therapies targeting the interleukin-23–interleukin-17 axis show promise in axial spondyloarthritis. Phase 3 trials have demonstrated the effectiveness of secukinumab, an anti-interleukin-17 inhibitor, in ankylosing spondylitis, leading to its approval in various regions. Although direct comparisons are lacking, secukinumab appears to offer response rates comparable to TNF-blockers for similar patient groups. It has also shown effectiveness in patients for whom TNF-blocker therapy failed or was discontinued. Nevertheless, the role of interleukin-17 inhibitors in axial spondyloarthritis treatment is still evolving as more clinical experience is gained.

A prospective open-label trial of ustekinumab, a monoclonal antibody against the p40 subunit of interleukin-12 and interleukin-23, has shown promise in ankylosing spondylitis and is undergoing further evaluation in ongoing placebo-controlled trials for both ankylosing spondylitis and non-radiographic axial spondyloarthritis.

Tofacitinib, an oral Janus kinase inhibitor, has shown a positive signal for clinical and MRI responses in ankylosing spondylitis in a phase 2 double-blind placebo-controlled study, requiring confirmation in larger trials. On the other hand, apremilast, an oral PDE4 inhibitor, demonstrated a moderate reduction in disease activity in a small proof of concept trial but did not show a superior response to placebo in a larger placebo-controlled trial for ankylosing spondylitis [20].

Conclusions

- Spondyloarthritis (SpA) is a group of inflammatory rheumatic disorders with shared features, genetic, and familial associations, characterized by the defining radiographic feature of sacroiliitis.
- Diagnostic criteria, such as those from the ASAS group, enable early identification of SpA before spine structural changes, with MRI updates in the new criteria for early axial SpA.
- Treatment options are continuously evolving, with TNF-alpha blocking agents and other biological treatments emerging as the primary therapeutic approaches, providing effective solutions.
- Future challenges include preventing new bone formation and spinal fusion, identifying early diagnostic measures, exploring novel treatment targets, and advancing efforts towards disease remission.

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Familial Mediterranean Fever

40

Yackov Berkun and Eli M. Eisenstein

Abstract

Familial Mediterranean fever (FMF), the most prevalent monogenic autoinflammatory disease (AID), is characterized by recurrent, self-limited episodes of fever and serositis. The most significant complication of FMF and cause of premature disease-associated mortality is amyloidosis, which can be prevented by prophylactic colchicine treatment. The diagnosis of FMF is often challenging, leading to delays in initiating appropriate treatment. Advances in molecular biology over the last decades have greatly improved the diagnosis and understanding of AID, revealing new syndromes and underscoring the crucial role of genetics in diagnosing FMF and other related conditions. However, this progress has also brought complexity due to the identification of numerous genetic variations associated with physiologically inappropriate activation of innate immunity. With similar symptoms presenting in various AID, well-defined diagnostic criteria play a vital role in ensuring accurate diagnosis and guiding proper medical management and interventions. In response to these challenges, diagnostic and classification criteria have been developed for AID in general, and FMF in particular. While their effectiveness can vary across diverse populations and patient groups, they collectively contribute to earlier and more precise diagnoses. However, further refinement and extensive validation efforts are needed to improve the clinical reliability of these criteria.

Keywords

Familial Mediterranean fever · MEFV gene · Autoinflammatory · Diagnostic criteria · Classification criteria · Innate immunity · Diagnosis

Introduction

Autoinflammatory diseases (AID) constitute a group of disorders marked by inflammation that appears to arise without evident infectious cause, autoantibodies, or autoreactive T-lymphocytes. These disorders usually lack a clear trigger for their inflammation, making their nature distinctive [1]. Most AID result from genetic defects within the innate immune system. Among these, Familial Mediterranean fever (FMF) stands out as the most prevalent monogenic AID [2]. It predominantly affects ethnic populations residing along the eastern Mediterranean coast, including Sephardic Jews, Armenians, Turks, and Arabs. FMF also occurs in other Mediterranean basin ethnicities and in patients in non-endemic areas. This disease manifests with sporadic, brief episodes of inflammation of serous membranes, accompanied by fever [3]. The most noteworthy complication associated with FMF is amyloidosis, a leading cause of mortality. Fortunately, this peril can be averted by prophylactic colchicine treatment, which is recommended for all FMF patients [4].

Advances in molecular biology over the last few decades have substantially improved the diagnosis and comprehension of AID. These advances have revealed novel syndromes and solidified genetics' pivotal role in diagnosing AID, including FMF. However, the landscape has grown more intricate due to the identification of a plethora of genetic variations associated with innate immunity. Because different AID may present with similar symptoms, well-defined diagnostic criteria play a pivotal role in ensuring precise diagnosis and guiding appropriate medical monitoring and intervention [5].

Clinical Manifestations

FMF is characterized by febrile episodes accompanied by manifestations of serositis: peritonitis, pleuritis, synovitis, sometimes coupled with erysipelas-like erythema and acute scrotum. These bouts, lasting about 3 days, are sporadic and

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self-resolving. Between attacks, patients are usually asymptomatic. Certain attacks might be triggered by factors such as emotional stress, physical activity, viral infections, or menstruation [3]. Most cases present before the age of 10, with a third of pediatric patients showing FMF symptoms before 2 years of age. Abdominal pain, besides fever, stands as the most prevalent FMF feature. It may be diffuse or localized and varies from mild to more characteristic severe pain with signs of peritonitis. Articular involvement constitutes the second most common FMF manifestation. Frequently acute, it typically targets a large joint in the lower extremities, sometimes persisting longer than other FMF symptoms. Pleural attacks, usually acute and one-sided, and erysipelas-like erythema (painful, hot, swollen, red skin lesions on the lower extremities) appear in a third of FMF patients during their lifetime. Scrotal attacks, affecting 10% of male patients, arise due to tunica vaginalis inflammation. Occasional FMF manifestations encompass pericarditis and prolonged febrile myalgia. Over the course of the disease, a patient might experience various attack forms, although a recurrence of the same type over years is more typical. In early life, FMF may manifest atypically with fever attacks alone, lacking serositis signs. Transitioning to the more typical disease with serositis symptoms might occur years later, implying that FMF in this age group is a disease in evolution [6].

Laboratory Findings

FMF attacks exhibit leukocytosis and elevated acute-phase reactants. These inflammatory markers assist physician to distinguish FMF attacks from other conditions, such as viral illness, fibromyalgia, functional abdominal pain, and irritable bowel syndrome. While most acute-phase reactants generally return to baseline levels between attacks, in some instances, they may persistently remain high, particularly in cases of severe or uncontrolled disease. Chronic clinically silent inflammation, manifested by elevated SAA levels between attacks may be found in up to 30% of patients. Proteinuria, an indicator of renal amyloidosis, may develop over years if FMF remains untreated. Therefore, regular treatment with colchicine and annual examination of inflammatory markers and urinary protein is recommended in all patients.

Amyloidosis and Other Long-Term Complications

Although categorized as periodic, FMF can bring about certain forms of more prolonged morbidity, including protracted febrile myalgia, FMF-associated vasculitis, and peritoneal adhesions that lead to intestinal obstructions and female infertility. The most severe long-term complication associated with FMF is amyloidosis, typically affecting the kidneys and potentially advancing to end-stage renal disease. These complications tend to manifest primarily in untreated or noncompliant patients and are linked to specific ethnicities, countries of residence, and MEFV mutations.

Genetics

To date, almost 400 MEFV sequence variants have been cataloged in Infevers (http://fmf.igh.cnrs.fr/ISSAID/infevers/), an online database of AID mutations [7]. The majority of these mutations are located in exon 10, which contains the four most common variants found in the majority of FMF patients: M694V, V726A, M680I, and M694I. Among these, the M694V mutation is linked with severe disease, resistance to colchicine treatment, and the development of amyloidosis. The role of E148Q, a sequence variant in exon 2, as a disease-causing mutation remains debated. Among a substantial cohort of Israeli children diagnosed with FMF, testing for common MEFV mutations detected two mutations in 60% of cases, while no mutations were identified in less than 10%. Interestingly, 30% of patients showing typical FMF symptoms and positive response to colchicine exhibited only a single mutation. While it was once assumed that these patients carried rarer MEFV mutations on the second allele of the gene, genomic sequencing has failed to identify a second mutation in this group [8]. Most individuals with a single MEFV mutation are asymptomatic carriers. However, classical FMF can indeed manifest in carriers with only one MEFV mutation, and conversely, individuals with two mutations may display no overt disease symptoms. Screening of a sample of the Israeli general population has shown that the number of individuals with unexpressed double-mutated *MEFV* exceeds the number of patients with overt FMF by several times [9]. These findings, combined with the variable expression of FMF disease, suggest a significant role of additional environmental factors or modifying genes in shaping the clinical presentation of FMF [10].

Diagnosis

In the past, FMF diagnosis relied on clinical symptoms, complemented by factors like ethnic background and family history. However, numerous patients, including children and those with mild symptoms, exhibited atypical attacks, leading to diagnostic challenges and treatment delays. Since the identification of the MEFV gene, molecular genetic testing has become a valuable diagnostic tool, particularly for atypical cases. When two pathogenic mutations are detected, FMF diagnosis is confirmed, prompting initiation of lifelong colchicine therapy. In patients with atypical attacks carrying one mutation (heterozygotes) or no mutations, genetic testing does not definitively support or rule out FMF. Instead, a 3–6 month trial of colchicine is recommended to assess whether there is a reduction in attack severity and frequency.

Diagnostic and Classification Criteria

Various sets of diagnostic criteria have been proposed. An early version by Sohar et al. [3] in 1967 outlined three essential criteria: (1) short fever episodes recurring at varying intervals; (2) painful manifestations in the abdomen, chest, joints, or skin accompanying the fever; (3) absence of any causative factor or pathologic finding, in vivo or postmortem, explaining the clinical picture. The other three criteria were optional: (4) amyloidosis, clinically of the nephropathic and anatomically of the perireticulin type; (5) evidence of autosomal recessive inheritance; (6) Mediterranean, and particularly Sephardic Jewish or Armenian origin. Shortly before the discovery of the FMF gene, widely used diagnostic criteria emerged at the Tel-Hashomer Medical Center in Israel (Table 40.1) [11]. These criteria introduced precise definitions of disease manifestations, along with prospective statistical evaluation in patient and control groups. As per the Livneh criteria, FMF diagnosis is suggested by the presence of at least 1 of 4 major criteria, 2 of 5 minor criteria, 1 minor criterion plus 5 of all 10 supportive criteria, or 4 of 5 specific supportive criteria. Another, simplified set of Livneh criteria, Tel-Hashomer criteria allows FMF diagnosis with one major criterion (recurrent typical attacks) or two minor criteria (incomplete attacks, exertional leg pain, and positive response to colchicine). Both sets demonstrate specificity and sensitivity exceeding 95%. Typical attacks are defined as recurrent, febrile episodes lasting 0.5–3 days. Incomplete attacks are similar painful and recurrent episodes but differ in one or two aspects (lack of fever, duration between 6 h to a week, abdominal pain without signs of peritonitis or localized pain, arthritis in unspecified joints). Although the Tel-Hashomer criteria were developed for Jewish adults, they are widely employed for diagnosing FMF in children and other ethnic groups. Their effectiveness in children has been assessed with varying results [12] (Table 40.2).

Table 40.1 Diagnostic and classification criteria for FMF

Livneh's criteria[a]	Tel Hashomer or simplified Livneh's criteria[b]	Yalcinkaya Ozen criteria[c]	Eurofever/PRINTO clinical + genetic criteria	Eurofever/PRINTO clinical only criteria[d]
Major criteria Typical attacks: 1. Peritonitis (generalized); 2. Pleuritis (unilateral) or pericarditis; 3. Monarthritis (hip, knee, ankle); 4. Fever alone	**Major criteria** Typical attacks: 1. Peritonitis (generalized); 2. Pleuritis (unilateral) or pericarditis; 3. Monarthritis (hip, knee, ankle); 4. Fever alone	6–72 h of duration >3 attacks: Fever, axillary >38C, abdominal pain; chest pain; oligoarthritis; FMF family history	Presence of confirmatory MEFV genotype and at least one of: Duration of episodes 1–3 days; arthritis; chest pain; abdominal pain	Eastern Mediterranean ethnicity Duration of episodes 1–3 days; arthritis; chest pain; abdominal pain
Minor criteria 1–3. Incomplete attacks involving: Abdomen, chest, joint; 4. Exertional leg pain 5. Favorable response to colchicine	**Minor candidate criteria** 1–2 Incomplete attacks in any of 1. Chest 2. Joint 3. Exertional leg pain 4. Favorable response to colchicine		**Or** Presence of not confirmatory MEFV genotype and at least 2 of: Duration of episodes 1–3 days; arthritis; chest pain; abdominal pain	Absence of aphthous stomatitis; urticarial rash or maculopapular rash; painful lymph nodes
Supportive criteria 1. Family history of FMF, 2. Ethnic origin, 3. Age <20 years at onset; 4–7. Attacks: Severe, requiring bed rest; spontaneous remission; symptom-free interval; inflammatory laboratory markers at attack; 8**.** Protein/hematuria; 9. Unproductive laparotomy or white appendix; 10. Consanguinity of parents				

[a] 1 major or 2 minor criteria, or 1 minor plus 5 supportive criteria
[b] 1 major or **2** minor
[c] 2 of 5 criteria
[d] ≥6 criteria

Table 40.2 Sensitivity and specificity of criteria in different case series

	Sag [18]	Demyrkaya [15]	Kondi [14]	Yalcinskaya [13]	Dingulu [17]	Onder [21]	Ekinki [20]	Aydin [19]	Tanatar [22]
FMF cohort, n	151 children	339 children	100 children	170 children, 2 mutations[a]	122	113 children	130 children, at least one mutation[a]	106 children, at least one mutation[a]	1291 children
Controls	82, AID	377, AID	40, fever recurrent	141, FMF symptoms	333, AID	117, FMF symptoms	41, AID	31, PFAPA	133, AID
Centers	Turkey, one	International, multicenter	France, one	Turkey, 4 centers	Multicenter Europe	Turkey, one	Turkey, one	Turkey, one	Turkey one
Sensitivity, %									
Tel Hashomer	89	45	99	99	nd	70	93	nd	83
Livneh	nd	77	nd	nd	nd	nd	nd	nd	99
Y	93	87	100	87	nd	89	98	98	92
E	96	nd	nd	nd	98	94	95	97	91
E clinical	nd	nd	nd	nd	91	nd	93	97	nd
Specificity, %									
Tel Hashomer	93	97	45	56	nd	96	90	nd	99
Livneh	nd	41	nd	nd	nd	nd	nd	nd	1
Y	84	40.7	50	94	nd	85	56	74	33
E	73	nd	nd	nd	29	90	83	97	100
E clinical	nd	nd	nd	nd	91	nd	80	nd	nd

[a] MEFV gene mutation

Yalcinskaya et al. [13] introduced pediatric criteria for diagnosing FMF in children, using these to evaluate a Turkish cohort. According to these criteria, diagnosis in children is confirmed with the presence of two of five clinical criteria: fever, abdominal pain, chest pain, arthritis (each lasting 6–72 h), and a family history of FMF. The cohort where these criteria were generated included only children genetically ascertained to have two *MEFV* mutations. Several Livneh criteria (age, ethnic origin, parental consanguinity) were excluded, as the cohort was restricted to children of Turkish ethnicity, where the rate of consanguinity is high. As a result, these criteria were formally applicable only to children carrying two MEFV mutations from a single ethnic group.

Kondi et al. [14] conducted a comparison between the pediatric and Tel-Hashomer criteria, studying a group of 100 French children (majority Sephardic Jews) with FMF and a control group of 40 patients affected by other recurrent fever syndromes. Both sets of criteria exhibited comparable high sensitivity, but displayed low specificity rates (45% and 50%, respectively). The authors emphasized that due to the potentially severe consequences of failing to diagnose FMF, prioritizing high sensitivity over high specificity is crucial. In another study involving a mixed Turkish group of adults and children with FMF carrying one MEFV gene mutation, both sets of criteria demonstrated substantial sensitivity rates [12].

Demirkaya conducted an analysis of the TH, Livneh, and pediatric criteria using a large cohort of 716 patients with AID from an international registry [15]. Among these, the pediatric criteria exhibited the highest sensitivity at 87%, yet demonstrated lower specificity at 41%. Remarkably, the Tel-Hashomer criteria displayed superior accuracy in distinguishing pediatric patients with FMF from those with other AID. The study's distinctiveness lay in its incorporation of a diverse array of patients from various ethnic backgrounds, as well as the inclusion of individuals with other AID as a control group.

All these criteria were established and performed effectively in populations with high FMF prevalence and they lacked consideration of the genetic data accumulated over time [3, 11, 13]. Their applicability to populations where the disease is infrequent, alongside the presence of other AID, received insufficient evaluation. To address these challenges, a recently formulated set of criteria for AID classification, including FMF, emerged [16]. These Eurofever/PRINTO classification criteria (EPCC) blend clinical manifestations with genotype information and are composed of two distinct sets: mixed and clinical-only, catering to patients with and without genetic data, respectively. The EPCC criteria demonstrated a sensitivity ranging from 85% to 89% and specificity from 94% to 100% for FMF. It is important to note that these criteria were crafted to categorize the five most prevalent AID and are recommended for patient inclusion in research studies, rather than for individual patient diagnoses [16].

The utility of these new criteria was scrutinized in several studies, with physician diagnosis serving as the gold standard benchmark [7, 17–22].

The Dingulu et al. study was pioneering in evaluating the effectiveness of the new EPCC in a multicenter European cohort consisting of 455 patients with hereditary AID, including 122 subjects with FMF [17]. Notably, the mixed clinical/genetic criteria displayed a high sensitivity of 98% for FMF but an unfortunately low specificity of 29%. Encouragingly, the mixed EPCC exhibited favorable performance for patients harboring at least one pathogenic mutation in the MEFV gene, combining clinical criteria for those with no mutation or unknown genotype, yielding a sensitivity of 81% and a specificity of 98%. However, the clinical criteria resulted in the misclassification of 28 patients with other AID as FMF. This led the authors to conclude that the clinical set of EPCC could not accurately classify patients when genetic tests for AID were lacking.

In the study by Sag E et al., a comparison of three different criteria within a group of 151 Turkish children with by FMF and 82 patients experiencing other periodic fevers followed in one clinic was done [18]. The new EPCC demonstrated the highest sensitivity at 96%, but the lowest specificity. Upon further analysis, the highest sensitivity of these criteria was observed in patients carrying two mutations in exon 10, whereas patients with only one mutation exhibited the lowest sensitivity. Integrating genetic data with clinical manifestations amplified the sensitivity of the new criteria; however, this resulted in decreased specificity and an elevated rate of controls being misclassified as FMF. In populations characterized by a high prevalence of MEFV mutation carriers, a noteworthy concern emerged: numerous patients with other AID might be inaccurately diagnosed as FMF. An advantage of EPCC lies in their clinical-only set, which can guide clinicians toward performing genetic testing for patients experiencing recurrent fevers [18].

Despite being an autosomal recessive disease, a third of FMF patients exhibit only a single MEFV mutation. A recent monocentric study in Turkey, comparing the new EPCC with pediatric criteria among children with FMF carrying a solitary exon 10 mutation, alongside a small group of PFAPA patients, revealed remarkably high sensitivities for both sets of criteria. Interestingly, contrary to findings of Sag study in the same population [18], the EPCC criteria show improved specificity (97%) when contrasted with the pediatric criteria's 74% [19].

In a study by Bustaffa et al., the impact of the EPCC was investigated in a cohort of 887 FMF patients from the multicenter Eurofever registry [7]. Notably, this cohort deviated from the norm, with fewer than 40% of participants displaying two pathogenic mutations in the MEFV gene, and almost 25% having no pathologic mutation at all. Sensitivity and specificity of these criteria were not assessed. Only 70% of FMF patients fulfilled the EPCC criteria. A significant portion of the EPCC-negative group lacked informative genetics, and almost a third were not treated with the standard colchicine therapy. It is crucial to note that while EPCC serves as classification criteria rather than diagnostic ones, other AID should be considered for these patients.

In a study by Ekinki et al., a genetically homogeneous cohort of children with FMF from a single Turkish center all possessing at least one M694V mutation was evaluated [20]. Here, all four criteria sets demonstrated excellent sensitivity. Notably, the Tel-Hashomer criteria and EPCC outperformed the less specific pediatric criteria in effectively distinguishing FMF from other AID. In another study, conducted in a similarly genetically uniform cohort of children from Turkey with at least one MEFV gene mutation, the control group diverged from most other studies using AID, by being consistent of children exhibiting clinical features that resembled FMF. Impressively, all three criteria sets performed well, with the Tel-Hashomer criteria being the most specific (96%) and the EPCC being the most sensitive (94%) [21].

In a comprehensive study led by Tanatar et al., the performances of all four criteria sets were assessed in an expansive cohort comprising 1291 children with FMF and 133 with various AID, all being cared for at a single Turkish rheumatology center [22]. The EPCC demonstrated the highest specificity, whereas the Livneh and pediatric criteria led to misdiagnoses of many AID patients as FMF. In a subanalysis with consideration for MEFV mutations all criteria performed well in diagnosing children with two mutations. However, both the EPCC and Tel-Hashomer criteria exhibited reduced accuracy when diagnosing patients with heterozygous mutations.

In summary, despite substantial strides in understanding and treating autoinflammatory diseases, there remains a considerable delay in their diagnosis. Various sets of diagnostic and classification criteria have been developed, and although their effectiveness may vary across different populations and cohorts, they collectively contribute to earlier and more precise FMF diagnoses. Nonetheless, further enhancements and extensive validation efforts are required to refine these criteria even further.

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VEXAS Syndrome

41

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Abstract

Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic (VEXAS) syndrome was described in 2020 as an autoinflammatory disease caused by postzygotic variants in the *UBA1* gene. VEXAS syndrome mostly occurs in adult males with a constellation of inflammatory manifestations, among which stand out recurrent fever, musculoskeletal complaints, auricular/nasal chondritis, neutrophilic dermatoses skin lesions, lung inflammatory infiltrates, venous thrombosis and different-sized vessel vasculitis. Laboratory tests are characterized by increased levels of acute-phase reactants and macrocytic anemia. At the bone marrow examination, myelodysplastic changes are frequent, and cytoplasmic vacuoles in myeloid and erythroid precursors in bone marrow are highly characteristic. Glucocorticoids at moderate-to-high doses are effective, but the remaining immunosuppressive (conventional or biological) drugs tend to show limited or absent efficacy. Azacitidine has been associated with a good response, particularly in patients with accompanying myelodysplastic syndrome. Allogeneic hematopoietic stem cell transplantation currently appears to be the only curative therapy for VEXAS syndrome. The wide spectrum of clinical presentations with a common difficult-to-treat disease characteristic of VEXAS syndrome is leading to a paradigm shift in certain hematologic conditions and systemic diseases, such as relapsing polychondritis, neutrophilic dermatoses and several types of vasculitis, which now have become part of VEXAS syndrome.

Keywords

VEXAS syndrome · Monogenic autoinflammatory diseases · Autoinflammation · Adult-onset · Mosaicism

VEXAS syndrome was described in 2020 as a complex monogenic autoinflammatory disease occurring exclusively

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in adult patients [1]. The acronym VEXAS includes the terms "Vacuoles" (intracytoplasmic) in myeloid and erythroid precursor cells (in the bone marrow), "E1 enzyme" initiating the ubiquitination process, "X-linked," "Autoinflammatory" disease and "Somatic" mutations in the *UBA1* gene [1].

Epidemiology

A 2023 prevalence study in an American population of 163,096 participants found variants in the *UBA1* gene in 11 individuals (nine men and two women with no evidence for aneuploidies), which corresponds to a prevalence of 7.4 cases (23.4 for men and 3.8 for women) per 100,000 people >50 years [2].

With regard to the subjects found carriers of *UBA1* mutations, all were symptomatic since 6 (54.5%) presented with systemic manifestations, all of them (100%) had anemia and in 10 (91%) anemia was macrocytic and also had thrombocytopenia [2].

Genetics and Pathophysiology

VEXAS syndrome is caused by postzygotic variants in the *UBA1* gene, located on the short arm of X chromosome, which encodes the E1 ubiquitin-activating enzyme. Although VEXAS syndrome was initially described as an X-linked disease exclusively affecting males, several females (usually patients with monosomy X) have been reported with this condition [2–4].

The most frequent mutations are missense variants affecting the methionine-41 (p.Met41) residue. Variants were described initially restricted to cells of the myeloid line, and therefore can be identified in circulating monocytes and neutrophils [1, 4–6]. However, postzygotic mutations in the *UBA1* gene have been identified also in nonhematopoietic tissues, such as nails [7]. Updated information on the identified variants and their genotype–phenotype correlation can be found at the Infevers Registry (https://infevers.umai-montpellier.fr/web/search.php?n=46).

The UBA1 protein is physiologically expressed as the two isoforms, the nuclear isoform (UBA1a) and the cytoplasmic isoform (UBA1b), which initiate translation at position p.Met1 and p.Met41, respectively. Mutations at p.Met41 generate a new cytoplasmic isoform (UBA1c) initiating translation at position p.Met67, with an ensuing defective function of the E1 enzyme and an abnormal initiation of the ubiquitination process [1]. Consequently, proteins are not properly ubiquitinated for being degraded by the cytoplasmic proteasome complex, which subsequently leads to cellular stress and activation of different inflammatory mechanisms, including multiple innate immune pathways, such as tumor necrosis factor (TNF), interleukin (IL)-6 and interferon gamma (IFNγ) [1]. These pathophysiological changes have been found in circulating monocytes and neutrophils, but absent in B and T lymphocytes from patients with VEXAS syndrome [1]. In the same sense, an *UBA1* gene-deficient zebrafish model found an abnormal development and premature death of the knockout animals compared to those not deficient, which was also associated with an increased expression of proinflammatory genes [1].

These findings suggest that the dysregulation and activation of different pathogenic pathways in VEXAS syndrome are involved in dysfunctional hematopoiesis and immune-inflammatory responses (not well known yet), with the resulting multisystem inflammatory involvement, which is characteristically refractory to multiple treatments in this disease.

Clinical Manifestations

VEXAS syndrome is presented in males between the ages of 45 and 80 years with complex and mixed systemic inflammatory and hematological manifestations. Table 41.1 illustrates the main clinical manifestations described in several series of patients with VEXAS syndrome [1, 6–8]. Persistent or periodic fever, weight loss and musculoskeletal manifestations, mainly arthralgia or arthritis, are frequent systemic manifestations. Cutaneous involvement is observed in 83–100% of patients as neutrophilic dermatoses (Fig. 41.1a), nodules, panniculitis, erythema nodosum, urticarial rashes, livedo racemosa and cutaneous vasculitis. Auricular (Fig. 41.1b) and nasal chondritis, vasculitis lesions affecting all vessel types and sizes (from aorta to small vessels), venous thrombosis or thromboembolism and lung infiltrates (Fig. 41.1c, d) are also frequent. Ocular inflammation (as uveitis, scleritis, episcleritis and orbital tumor), and different organ involvement, including renal, testicular, cardiac, gastrointestinal tract, central and peripheral nervous system, as well as lymphadenopathy, hepatomegaly and splenomegaly, have been described [1, 6–8]. About half of patients exhibit concomitant hematological abnormalities, among which myelodysplastic syndrome (MDS) is predominant [6, 8].

VEXAS syndrome has a poor prognosis, with a mortality ranging from 15.5% to 40%, mainly due to disease progression and infections favored by sustained immunosuppression [1, 6–8].

Table 41.1 Clinical manifestations of patients with VEXAS syndrome

Characteristics	Beck et al. [1] *N* (%)	Bourbon et al. [8] *N* (%)	Georgin-Lavialle et al. [6] *N* (%)	Mascaró et al. [7] *N* (%)
Number of patients	**25**	**11**	**116**	**30**
Male	25 (100)	11 (100)	111 (95.7)	30 (100)
Age at the time of diagnosis (years); *median [IQR] or (range)*	–	–	71 [66–76]	–
Age at symptoms onset (years); *median [IQR] or (range)*	64 (45–80)	66 (47–83)	67 [62.5–73]	67.5 (52–86)
Previous diagnoses				
Relapsing polychondritis	15 (60)	5 (46)	–	–
Neutrophilic dermatosis	8 (32)	5 (46)	–	–
Vasculitis	4 (16)	7 (64)	–	–
Myelodysplastic syndrome	6 (24)	6 (55)	58 (50)	–
MGUS/multiple myeloma	5 (20)	1 (9)	12 (10.3)	–
RA/adult-onset still disease	–	2 (18)	–	–
Mortality	10 (40)	3 (27)	18 (15.5)	12 (40)
Systemic manifestations				
Weight loss	14 (56)	6 (55)	62 (54.5)	–
Fever	23 (92)	10 (91)	75 (64.7)	20 (66.7)
Arthritis/arthralgia	17 (68)	11 (100)	33 (28.4)	16 (53.3)
ENT manifestations				
Chondritis	16 (64)	5 (46)	42 (36.2)	16 (53.3)
Auricular	16 (64)	5 (46)	37 (31.9)	16 (53.3)
Nasal	12 (48)	1 (9)	18 (15.5)	6 (20)
Sensorineural hearing loss	10/16 (63)	1 (9)	–	–
Cutaneous lesions	22 (88)	11 (100)	97 (83.6)	27 (90)
Neutrophilic dermatosis/plaques	9 (36)	7 (64)	46 (39.6)	20 (66.7)
Nodules/panniculitis/erythema nodosum	13 (52)	4 (36)	15 (12.9)	9 (30)
Urticaria/Papular exanthema	–	–	35 (21.5)	9 (30)
Purpura/Vasculitis	–	6 (55)	30 (25.9)	14 (46.7)
Livedo racemosa	–	–	–	7 (23)
Periorbital edema	4 (16)	1 (9)	10 (8.6)	8 (26.7)
Gastrointestinal	–	–	16 (14.0)	–
Peripheral nervous system	–	1 (9)	17 (14.7)	–
Ocular (uveitis, scleritis, episcleritis, orbit mass)	7 (28)	6 (55)	47 (40.5)	17 (56.7)
Cardiac	–	–	13 (11.2)	–
Pericarditis/pericardial effusion	1 (4)	–	5 (4.3)	–
Myocarditis	1 (4)	2 (18)	3 (2.6)	–
Pulmonary	18 (72)	–	57 (49.1)	20 (66.7)
Infiltrates	18 (72)	5 (46)	47 (40.5)	16 (53.3)
Pleural effusion	8 (32)	–	11 (9.5)	–
Vascular				
Arterial (aortitis/aneurysms/thrombosis)	–	1 (9)	12 (10.3)	4 (13.3)
Venous thrombosis/thromboembolism	11 (44)	4 (46)	41 (35.3)	12 (40)
Renal	–	1 (9)	11 (9.5)	–
Polyadenopathy	–	5 (46)	40 (34.5)	–
Splenomegaly	9 (36)	3 (27)	16 (13.8)	–
Hepatomegaly	–	2 (18)	9 (7.8)	–

ENT Ear, nose and throat, *MGUS* Monoclonal gammopathy of unknown significance, *RA* Rheumatoid arthritis, *VEXAS* vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic

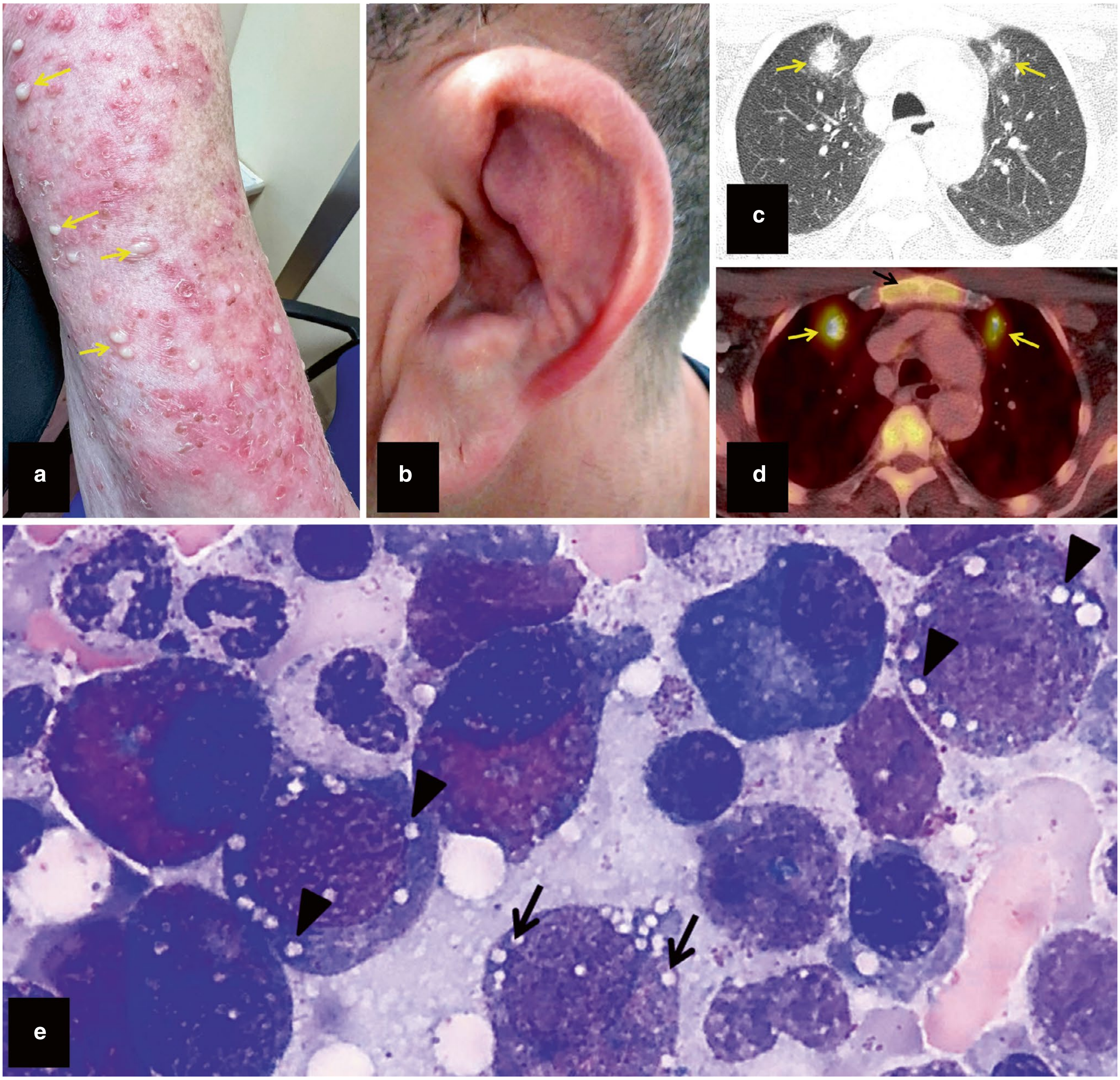

Fig. 41.1 Clinical, radiologic and hemopathological features of VEXAS syndrome. (**a**) pustular skin lesions with noninfectious folliculitis in lower limbs (arrows); (**b**) auricular chondritis; (**c**) bilateral pulmonary infiltrates in upper lobes (arrows) by computed tomography (CT); (**d**) hypermetabolic lung infiltrates in the same locations (arrows) by positron emission tomography (PET)-CT scan; (**e**) bone marrow aspiration showing cytoplasmic vacuoles in the myeloid (arrows) and erythroid (arrowheads) precursor cells

Laboratory Features

VEXAS syndrome is characterized by a prominent increase of acute phase reactants levels, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [1, 5–7]. Macrocytic anemia with a remarkably high mean corpuscular volume (MCV) and normal values of folic acid and vitamin B12 is almost invariably observed. Thrombocytopenia, leukopenia, lymphopenia and monoclonal gammopathy are also frequently detected [1, 5, 6, 8]. Positivity for autoantibodies such as rheumatoid factor and lupus anticoagulant has been observed in some patients [1, 5]. VEXAS syndrome has also been associated with antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis [9]. Laboratory values most commonly associated with VEXAs syndrome are detailed in Table 41.2.

Table 41.2 Laboratory changes of patients with VEXAS syndrome

Laboratory parameters Median [IQR] or (range)	Beck et al. [1]	Georgin-Lavialle et al. [6]	Ferrada et al. [5]	Mascaró et al. [7]
Number of patients	**25**	**116**	**13**	**30**
ESR (mm/1 h)	97 (64–124)	–	66.5 [42–110]	78.5 (2–141)
CRP (g/dL)	73 [18–128]	6.1 [3–12.8]	1.8 [1–10]	–
Ferritin (ng/mL)	–	–	–	1163 (54–11,931)
Hemoglobin (g/dL)	9[a]	10.1 [9–11.5]	10 [8–12]	9.9 (5.9–16.1)
MCV (fL)	110[a]	101 [94–107]	105 [102–115]	105 (85–133)
Platelets ($\times 1000/\text{mm}^3$)	110[a]	204 [138–260]	145 [100–169]	151 (4–753)
Leucocytes (n/mm^3)	4500[a]	4400 [2972–6222]	–	5900 (200–33,300)
Neutrophils (n/mm^3)	2500[a]	2600 [1640–4185]	–	–
Lymphocytes (n/mm^3)	600[a]	–	920 [500–1200]	–
Rheumatoid factor (positive)	5 (20)	–	4 (31)	–
Lupus anticoagulant (positive)	12 (48)	–	7 (54)	–

[a] Approximate mean values extracted from the Fig. S3 of the original study [1]

CRP C-reactive protein, *ESR* Erythrocyte sedimentation rate, *MCV* Mean corpuscular volume, *VEXAS* vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic

Hematopathology and Histopathology

Bone marrow aspiration in patients with VEXAS syndrome has generally reported as hypercellular, with a predominance of myeloid hyperplasia and dysplastic changes. Cytoplasmic vacuoles in myeloid and erythroid precursor cells (blasts, promyelocytes and proerythroblasts) have been identified in all cases (Fig. 41.1e) [1, 10]. Vacuoles have also been observed in eosinophils, monocytes, plasma cells and megakaryocytes [10]. The presence of cytoplasmic vacuoles in myeloid and erythroid precursor cells can be considered highly suggestive of VEXAS syndrome [1, 10], or even a pathognomonic finding in patients who do not have a different underlying hematological disease and have not suffered from any chemotherapy-induced myelotoxicity. Changes of MDS have been observed in about half of patients with VEXAS syndrome, and a lower proportion of them can be diagnosed with multiple myeloma [6, 8].

Biopsies of other affected territories may corroborate the presence of vascular inflammation supporting the diagnosis of systemic vasculitis. In particular, a skin biopsy may confirm the diagnosis of vasculitis, panniculitis or neutrophilic dermatosis [1, 3, 9].

Imaging Techniques

Computed tomography (CT) and magnetic resonance imaging (MRI) with angiographic study (when necessary) can provide information about tissue damage and type and extent of the vascular lesions in patients with VEXAS syndrome and neurological, hepatic, renal, pulmonary, cardiac, gastrointestinal or limb involvement. The detection of active inflammatory lesions, such as pulmonary infiltrates (Fig. 41.1c, d), vasculitis changes, visceromegaly and lymphadenopathy, can be confirmed by positron emission tomography (PET) with 18-fluorodeoxyglucose combined with CT (PET-CT) [3].

Differential Diagnosis

The differential diagnosis of VEXAS syndrome should be considered in adult males with systemic inflammatory manifestations and hematological abnormalities, both refractory to different immunosuppressive treatments. Maybe due to its recent description and the low level of knowledge and awareness among the medical community, a considerable number of patients reported with VEXAS syndrome had previously been diagnosed with systemic inflammatory or autoimmune diseases, chronic hematological disorders or a combination of these clinical situations. Therefore, differential diagnosis of VEXAS syndrome should include:

(a) Systemic autoimmune diseases: relapsing polychondritis, cutaneous leukocytoclastic vasculitis and systemic vasculitis (such as polyarteritis nodosa, cutaneous arteritis, giant-cell arteritis, Behçet's disease, cryoglobulinemic vasculitis and ANCA-associated vasculitis), rheumatoid arthritis and other undifferentiated arthritis.
(b) Neutrophilic dermatoses or panniculitis: Sweet's syndrome, extrapulmonary sarcoidosis and autoinflammatory diseases (with or without known genetic origin).
(c) Chronic hematological diseases: MDS, monoclonal gammopathy of uncertain significance, multiple myeloma and some types of lymphomas.

Systemic Inflammatory Diseases with a New Scenario After VEXAS Syndrome Discovery

Relapsing Polychondritis

Relapsing polychondritis is present in 36% to 64% of patients with VEXAS syndrome (Table 41.1) [1, 8]. A 2021 international study of 92 patients diagnosed with relapsing polychondritis detected postzygotic variants in the *UBA1* gene in 7.6% of cases [5]. Being a male patient, with an age >45 years at disease onset, presenting with fever, auricular chondritis, skin inflammation, deep vein thrombosis and pulmonary infiltrates were clinical features significantly associated with VEXAS syndrome [5]. In contrast, laryngeal, tracheobronchial or costal chondritis were not observed in VEXAS syndrome. With regard to laboratory changes of patients with relapsing polychondritis, those with VEXAS syndrome presented more commonly with elevated acute phase reactant levels, macrocytic anemia, thrombocytopenia and lymphopenia. Patients with VEXAS syndrome had also been diagnosed more frequently with MDS, monoclonal gammopathy of unknown significance and multiple myeloma than those with isolated relapsing polychondritis [5]. Based on these results, the authors proposed a diagnostic algorithm for VEXAS syndrome consisting in three criteria: (a) being male; (b) having a MCV of red blood cells >100 fL; and (c) a platelet count <200,000/mm^3 [5]. The fulfillment of the three criteria was associated with 100% sensitivity and 96% specificity for the identification of pathogenic variants in the *UBA1* gene in those patients previously diagnosed with relapsing polychondritis [5].

Systemic Vasculitis

The present or previous occurrence of a systemic vasculitis has been reported in 16% to 64% of patients with VEXAS syndrome [1, 6, 8]. Cutaneous vasculitis, especially in the isolated form of leukocytoclastic vasculitis, is the vasculitis most often associated with VEXAS syndrome, followed by polyarteritis nodosa and other single-organ and systemic vasculitides, such as aortitis, central nervous system vasculitis, giant-cell arteritis, Behçet's disease, cryoglobulinemic vasculitis and ANCA-associated vasculitis [1, 6, 8, 9].

In a retrospective study of 147 patients with vasculitis seen in a reference center, VEXAS syndrome was suspected in seven (5%) patients and could be genetically confirmed in three (2%) cases [9]. Five of the seven (71.4%) patients were also diagnosed with MDS. Previous diagnoses of the three patients with a genetically-proven disease were relapsing polychondritis, ANCA-associated vasculitis and undifferentiated autoinflammatory disease [9].

Monogenic Autoinflammatory Diseases

Monogenic autoinflammatory diseases, such as familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndromes (CAPS), Blau syndrome and deficiency of adenosine deaminase 2 (DADA2), have typically their onset at pediatric age. However, they may be occasionally manifested during adulthood with differences in clinical presentation compared to children [3, 11]. Pediatric patients tend to present with more intense and severe disease manifestations, have an increased risk of developing long-term complications, such as secondary amyloidosis, and disease is more often caused by pathogenic variants. Monogenic autoinflammatory diseases in adult patients have been reported with overlapping and less severe symptoms, lower risk of developing amyloidosis, and higher frequency of carrying variants of uncertain significance (VUS), nonconfirmatory genotypes and somatic or postzygotic variants [3, 11–13].

However, and similarly to what occurs in VEXAS syndrome, postzygotic variants in genes related to autoinflammation had been previously associated with complete or severe presentations of several monogenic autoinflammatory diseases in adult patients, such as CAPS, TRAPS, Blau syndrome and NLRC4-associated autoinflammatory disease [3]. With regard to overt cases of CAPS caused by postzygotic variants in the *NLRP3* gene, several patients have been reported starting symptoms above 40 years of age with fever, urticarial rash and sensorineural deafness, with some of them also presenting ocular or central nervous system involvement, and developing secondary amyloidosis [14].

The discovery in 2014 of DADA2 and STING-associated vasculopathy of interferon genes 1 (SAVI) syndrome as two types of vasculitis/vasculopathy of a genetic cause represented a conceptual revolution in the field of primary or idiopathic systemic vasculitides and monogenic autoinflammatory diseases [3, 11]. These autoinflammatory vasculitides are typical of the early childhood, but have also been described to occur in adult patients [11]. In this sense, the advent of VEXAS syndrome has added some practical implications on a daily basis, mainly in the diagnostic process of systemic vasculitis in adult patients. In appropriate complex clinical settings, genetic studies may contribute to confirm or rule out these monogenic autoinflammatory diseases.

Prognostic Factors in VEXAS Syndrome

A retrospective study (previous to the description of VEXAS syndrome) of 142 patients (61% female) diagnosed with relapsing polychondritis identified several factors associated with increased mortality [15]. These poor prognostic factors included male sex, cardiac abnormalities and development of MDS or other hematologic malignancy. While mortality of patients with tracheobronchial chondritis (not present in VEXAS syndrome) was of 13%, it was of 58% in patients with associated MDS (probably with undiagnosed VEXAS syndrome) [15].

A French multicenter registry of 116 patients with VEXAS syndrome identified three groups with different 5-year survival, with an overall mortality rate of 15.5% [6]. Factors associated with a concomitant MDS were the presence of recurrent fever, arthralgia, gastrointestinal tract involvement and pulmonary infiltrates. The group with constitutional symptoms, higher CRP levels and a lower frequency of chondritis (37%) had a mortality of 10.4%. Patients with MDS (16%) had the worst prognosis, with a mortality of 49.5%. Patients of the intermediate group (47%) had a mortality rate of 15.8% [6]. This study also identified the UBA1 p.Met41Leu mutation as associated with better outcomes [6].

Treatment

Data about therapeutic agents used and their efficacy in VEXAS syndrome is scarce and based on retrospective cases and small series with relatively short follow-up to correctly evaluate sustained responses. Among all immunosuppressive drugs used in VEXAS syndrome, glucocorticoids at high doses have proved efficacy in almost all cases. However, this positive effect is usually transient after tapering, since prednisone doses <10–20 mg/day are not usually effective [1, 3, 6, 9, 16]. Other immunomodulatory drugs (e.g., hydroxychloroquine, dapsone, colchicine and intravenous immunoglobulins), conventional immunosuppressive drugs (e.g., azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide) or biologic agents (e.g., TNF [infliximab, adalimumab, etanercept, golimumab], IL-1 [anakinra, canakinumab], IL-6 [tocilizumab], IL-17 [secukinumab], IL-12/23 [ustekinumab], CTLA-4 [abatacept] and CD20 [rituximab] blockers) have all obtained inconsistent or partial responses in VEXAS syndrome [1, 3, 6, 8, 9, 16]. Janus kinase (JAK) inhibitors, such as baricitinib (anti-JAK1/2) [1], tofacitinib and upadacitinib (anti-JAK1/3), and abrocitinib and filgotinib (anti-JAK1), have been similarly associated with partial or null responses [1, 3, 8, 16]. However, ruxolitinib (anti-JAK1/2) has been reported of some benefit in some isolated cases and in a series of 12 patients, maintaining clinical and biological responses in 75% and 33% of patients, respectively, after the first 6 months of treatment [17].

Hypomethylating agents, such as azacitidine and decitabine, have shown good and sustained effects, particularly in those patients with VEXAS syndrome and MDS [3]. In some patients, clinical and biological improvement has been proved to be associated with a progressive and remarkable decrease of the mutant UBA1 allele in peripheral blood [7].

Finally, allogeneic hematopoietic stem-cell transplantation (HSCT) has proved to be the only potential curative therapy in small series and isolated reports of VEXAS syndrome [3]. However, a UK registry with four patients with VEXAS syndrome undergoing HSCT for hematological indications showed complete response in two (50%) patients, and two (50%) patients died for infectious complications [18].

Future Perspectives and Diagnostic/Classification Criteria for VEXAS Syndrome

Knowing the reason why somatic mutations in blood cells and clonal hematopoiesis associated with chronic myelodysplastic, myeloproliferative or lymphoproliferative diseases may finally cause an increased systemic inflammatory response will contribute to better understand the etiopathogenesis autoinflammatory diseases. For these new mixed clinical situations, the term "hematoinflammatory diseases" has been proposed [19].

Besides VEXAS syndrome diagnostic algorithm generated for patients with a previous diagnosis of relapsing polychondritis [5], well-defined classification and/or diagnostic criteria covering the broad spectrum of VEXAS syndrome phenotypes with different predominant manifestations, including neutrophilic dermatoses, vasculitis of different vessel sizes and hematologic abnormalities, mainly myelodysplastic syndromes, are still needed.

Randomized clinical trials with different agents, including proinflammatory cytokines blockers, JAK inhibitors and hypomethylating agents are definitely needed to better determine the real response rate and the phenotypes in which these drugs could be particularly useful. Because the old age of some patients with VEXAS syndrome may be a limiting factor to undergo allogeneic HSCT, to answer the question of which patients will benefit from HSCT, a phase II clinical trial studying the safety of allogeneic bone marrow transplantation in patients with VEXAS syndrome is currently ongoing (ClinicalTrials.gov identifier: NCT05027945).

Existing international multicenter registries contributing to increase knowledge about clinical, etiopathogenic and therapeutic aspects of VEXAS syndrome [20] may also assist in the development of classificatory/diagnostic criteria, which indeed would promote clinical trials to improve the current therapeutic options in this complex autoinflammatory disease.

Conclusions

VEXAS syndrome is a monogenic autoinflammatory disease caused by postzygotic variants in the *UBA1* gene affecting adult males. Its clinical presentation is characterized by different systemic inflammatory manifestations, increased markers of acute phase response and cytopenias, among which macrocytic anemia is constantly present. MDS and other hematological malignancies can coexist and cytoplasmic vacuoles in myeloid and erythroid precursor cells in bone marrow are characteristic. Medium-to-high doses of glucocorticoids is the only effective immunosuppressive treatment but insufficient to maintain response after tapering. Most of the remaining conventional and biological immunosuppressive drugs have showed a limited or absent efficacy. Hypomethylating agents have shown sustained beneficial effects, particularly in patients with accompanying MDS, and allogeneic HSCT seems to be the only curative therapy at this moment.

The discovery of VEXAS syndrome has represented a paradigm shift in monogenic autoinflammatory diseases, since they usually predominated in the pediatric age and somatic mutations were known to be associated with milder clinical forms than those caused by germline variants. In addition, VEXAS syndrome has led to reconsider different difficult-to-treat systemic diseases with which this complex inflammatory disease is usually confounded, including relapsing polychondritis, neutrophilic dermatoses and different types of vasculitis, as well as several hematologic disorders with an accompanying inflammatory phenotype.

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Fibromyalgia

42

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Abstract

FM has long been a controversial entity among clinicians and raised a diagnostic challenge. The following chapter reviews the progression of the FM criteria. The initial ACR 1990 criteria focused on the determination of chronic widespread pain and included both primary and secondary FM. Its main limitations were the difficulty of applying to clinical practice and exclusion of associated symptoms from the diagnosis.

The 2010 and 2011 criteria, in order to resolve these issues, eliminated the tender point exam as a requirement for diagnosis and included accompanying non-pain-related symptoms as an integral part of the diagnosis. However, the criteria failed to include patients with secondary FM.

The revised 2016 criteria altered the definition of generalized pain to avoid inclusion of patients with regional pain syndromes, as occurred in the 2010/2011 criteria. Additionally, it allowed the diagnosis of FM irrespective of other diagnosis, similarly to the 1990 ACR criteria.

Finally, the AAPT Criteria's multidimensional approach was adopted in order to allow the identification of the syndrome in clinical practice. It focuses on widespread pain as the core criteria, and other aspects act as confirmatory factors. However, the AAPT criteria had the worst performance with a sensitivity of 73.8% compared to 79.8% and 78% for the ACR 2011 criteria and ACR 2016 criteria, respectively.

Further research is required to allow a more accurate and convenient diagnosis of FM in clinical practice.

Keywords

Fibromyalgia · Classification · Diagnostic criteria · Diagnosis · Widespread pain · Generalized pain · Somatic symptoms

Prior to the establishment of the 1990 ACR Classification Criteria, several criteria sets were established. None of them had been clinically validated, nor were they based on a firm definition of fibromyalgia (FM), resulting in inconsistencies and with a diagnosis, which was primarily influenced by the developer's perception of the syndrome. The first ever-formal criteria lead to the validation of the FM diagnosis, and in 1992, fibromyalgia syndrome (FMS) was recognized by both the International Classification of Diseases (ICD) and the World Health Organization (WHO).

The American College of Rheumatology 1990 Classification Criteria

Early understandings of FM defined it as a chronic widespread pain disorder with other associated symptoms [1, 2]. In 1990, the American college of Rheumatology (ACR) approved for the first time its classification criteria of FM via a multicenter study that was entirely based on the determination of chronic widespread pain (CWP) ignoring the role and significance of associated symptoms to the FM construct [3].

According to this ACR classification, the diagnosis of FM required both of the following criteria to be satisfied:

1. Pain, defined as mild or greater in severity, in at least 11 of 18 predefined tender points on digital palpation;
2. Widespread musculoskeletal pain persisting for at least 3 months. Widespread pain was defined as axial plus upper and lower segment, plus left- and right-sided pain (Fig. 42.1).

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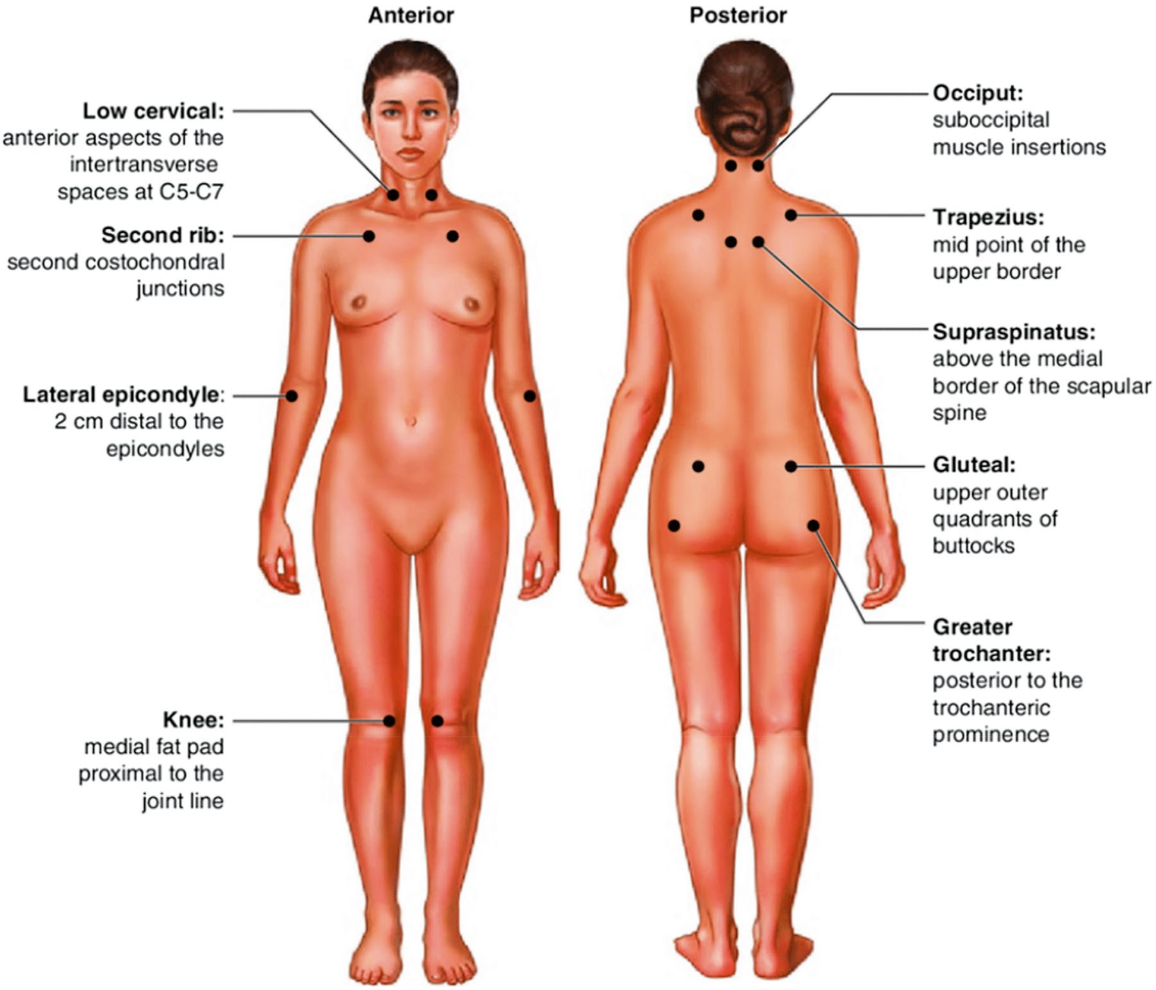
Anterior
Posterior
Low cervical: anterior aspects of the intertransverse spaces at C5-C7
Second rib: second costochondral junctions
Lateral epicondyle: 2 cm distal to the epicondyles
Knee: medial fat pad proximal to the joint line
Occiput: suboccipital muscle insertions
Trapezius: mid point of the upper border
Supraspinatus: above the medial border of the scapular spine
Gluteal: upper outer quadrants of buttocks
Greater trochanter: posterior to the trochanteric prominence

Fig. 42.1 Illustration demonstrating the anatomical location of the tender points assessed in fibromyalgia

This combination had a sensitivity of 88.4% and a specificity of 81.1% and could be applied to all subtypes of FM, primary and secondary appearing with other chronic rheumatic and other illnesses.

The study that lead to the development of these criteria included the population of secondary-concomitant FM and chosen controls which presented the same primary disorder but without FM. Thus, the criteria were able to provide a diagnosis of FM independent of other rheumatologic conditions [3].

Over the years, the 1990 criteria presented several difficulties. Although the ACR 1990 criteria helped to advance research studies of FM, it was impractical and not intended for clinical practice as it did not include associated symptoms, and required a tender point exam, which was difficult to perform in some clinical settings. In addition, the tender point exam was an inaccurate measure of hyperalgesia due to influence by subjective distress. Moreover, the exclusion of key features associated with FM, such as fatigue, sleep disturbances, cognitive symptoms, and various somatic symptoms, questioned its appropriateness in clinical life. In addition, when applied to clinical practice, the tender point count was found to be impractical, and therefore, uncommonly performed in primary care or incorrectly performed. The 1990 criteria did not perceive FMS as a spectrum, and as a result, failed to discover patients that were on the continuum within the spectrum, leading to their underrepresentation as FM patients. These 1990 criteria strongly skewed the gender distribution turning FM to be acknowledged as a female-related disorder, and finally, it failed to include and categorize patients who previously fulfilled the criteria, but over time experienced an improvement in their symptoms.

The 2010 Fibromyalgia Diagnostic Criteria

When presented in 2010, Wolfe et al. [4] stated the following criteria were not meant to replace the ACR classification criteria, but merely to address some of the difficulties in their clinical application.

Table 42.1 Fibromyalgia diagnostic criteria 2010 [4]

Criteria			
A patient satisfies diagnostic criteria for fibromyalgia if the following three conditions are met:			
1. Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥ 5 or WPI 3–6 and SS scale score ≥ 9.			
2. Symptoms have been present at a similar level for at least 3 months.			
3. The patient does not have a disorder that would otherwise explain the pain.			
Ascertainment			
1. WPI: Note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19.			
Shoulder girdle, left	Hip (buttock, trochanter), left	Jaw, left	Upper back
Shoulder girdle, right	Hip (buttock, trochanter), right	Jaw, right	Lower back
Upper arm, left	Upper leg, left	Chest	Neck
Upper arm, right	Upper leg, right	Abdomen	
Lower arm, left	Lower leg, left		
Lower arm, right	Lower leg, right		
2. SS scale score:			
Fatigue			
Waking unrefreshed			
Cognitive symptoms			
For each of the three symptoms above, indicate the level of severity over the past week using the following scale:			
0 = no problem			
1 = slight or mild problems, generally mild or intermittent			
2 = moderate, considerable problems, often present and/or at a moderate level			
3 = severe: Pervasive, continuous, life-disturbing problems			
Considering somatic symptoms in general, indicate whether the patient has:*			
0 = no symptoms			
1 = few symptoms			
2 = a moderate number of symptoms			
3 = a great deal of symptoms			
The SS scale score is the sum of the severity of the three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12			

[*] Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms

With the establishment of the 2010 and 2011 criteria [5], the definition of FM moved from a chronic pain disorder to a multisymptom disorder which included on the one hand the elimination of the tender point exam as a requirement for diagnosis, and on the other hand, it recognized the paramount importance of non-pain elements of FM that were included as part of the criteria for the disorder. The criteria are composed of two variables, the Widespread Pain Index (WPI), which strongly correlates with the tender point count, and the Symptom Severity (SS) scale, that best identified patients diagnosed with the ACR classification criteria.

The SS scale includes two parts, the first part of which evaluates the severity of fatigue, waking unrefreshed, and cognitive symptoms on a scale of 0–3, and the second part assesses the number of somatic symptoms present from a list of 41 symptoms. The SS score is derived from the sum of the two components (Table 42.1).

According to these criteria, the diagnosis of FM required a WPI ≥ 7 and an SS ≥ 5 or a WPI 3–6 and an SS ≥ 9. The latter option, which allows a diagnosis to be made with a lower WPI when accompanied by higher SS scores, reflects the importance attributed to the presence of additional non-pain symptoms in the new definition of FM.

The SS scale alone can be useful in assessing the symptoms severity of FM patients over time, even if along the course of the disorder, patients improve and fail to meet diagnostic criteria [4].

There are some similarities between the diagnostic criteria and another set of criteria that were proposed by Yunus et al. in 1981 [6], as both put more emphasis on the presence of accompanying symptoms, than the number of tender points.

The value of the 2010 criteria was demonstrated as approximately 25% of diagnosed FM patients did not satisfy the ACR 1990 classification criteria. A possible explanation for this discrepancy may be the change in the perception of the FM syndrome, increasing emphasis on important symptoms, rather than the tender point count alone.

However, patients with inflammatory rheumatic disorders, active cancer, fractures, defined neuropathic causes of pain, or other non-rheumatic causes for pain were excluded from the study. Therefore, these criteria may have missed patients with secondary-concomitant FM, which were represented in the previous criteria [1].

Similarly to the ACR criteria, the FM diagnosis was based on physician assessments and the symptoms' duration of at least 3 months was required.

In summary, this abovementioned criterion correctly classified 88.1% of the cases and did not any physical or tender point examination. The SS scale provides additional value by allowing the longitudinal evaluation of patients, with both current and previous FM [4].

Despite the emphasis of the 2010/2011 criteria of importance of associated symptoms, it is possible there had been too much movement away from chronic pain as the core symptom of FM [10]. Other studies of alternative criteria evaluated various associated symptoms along with a variety of definitions of widespread pain in the diagnosis of FM [7, 8]. As a result, the 2010 criteria created some controversy and confusion, and since 2010, alternative approaches as well as numerous studies have been performed to test validation. In addition, clinical research and clinical use have identified necessary areas for future updates in order to address certain problems, which have been noted.

The 2016 Revised Criteria

The authors of the revised 2016 criteria [9] have addressed various problems of the 2010/2011 criteria and provide further updates in order to improve the diagnosis of FM.

Firstly, as shown in Table 42.3, Widespread pain (WPI) is ≥7 and symptoms severity scale (SSS) score ≥ 5 or WPI 4–6 and SSS score ≥ 9″ (WPI minimum must be ≥4 instead of previous ≥3). Secondly, the 2016 criteria require that patients have "generalized pain," which is distinguished from the 1990 definition of "widespread pain." Generalized pain is defined as pain in four out of five regions. This aims to avoid the misclassification of patients and ensure that regional pain syndromes are not captured by the criteria as occurred in 2010/2011 criteria as it misclassified a small fraction of patients who did not have generalized pain [9]. Misclassification occurred because the WPI, while indicating the number of painful sites, did not consider the spatial distribution of the painful sites [9].

According to the 2010/2011 criteria, those meeting requirements for FM can't be distinguished from other chronic illnesses such as fatigue and irritable bowel syndrome if patients meet criteria for FM as well. The 1990 criteria stated: "a diagnosis of fibromyalgia remains a valid construct irrespective of other diagnosis" [9]. The 2010/2011 criteria stated that fibromyalgia could be diagnosed provided "The patient does not have a disorder that would otherwise explain the pain" (2010) and "The patient does not have a disorder that would otherwise sufficiently explain the pain" (2011) [4, 5]. The 2016 criteria adopted to endorse and accept the original 1990 recommendation that "fibromyalgia remains a valid construct irrespective of other diagnoses" [1]. This showed an important point on the specificity that anyone who satisfies the FM criteria can be classified to have the disorder and there is no possibility of misclassification. Therefore, a diagnosis of FM is met as long as FM criteria are satisfied, irrespective of another diagnosis, nor does it exclude the presence of other clinically important conditions.

Another change of the revised 2016 criteria is the recommendation for the use of the fibromyalgia symptom scale (FS scale). The symptoms criteria of the 2016 modification may vary in severity, just as the WPI. When applied clinically, the WPI and SSS can combine into the FS score which ranges from 0 to 31 (most severe). The FS scale acts a guide to estimate the FM criteria status and its' severity (Table 42.2) [9].

Table 42.2 Fibromyalgia criteria 2016 revisions [9]

Criteria		
A patient satisfies modified 2016 fibromyalgia criteria if the following three conditions are met:		
1. Widespread pain index (WPI) ≥ 7 and symptom severity scale (SSS) score ≥ 5 OR WPI of 4–6 and SSS score ≥ 9 2. Generalized pain, defined as pain in at least four of five regions, must be present. Jaw, chest, and abdominal pain are not included in generalized pain definition 3. Symptoms have been generally present for at least 3 months 4. A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses		
Ascertainment		
1. WPI: Note the number of areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19.		
Left upper region (Region 1)	*Right upper region (Region 2)*	*Axial region (Region 5)*
Jaw, left[a]	Jaw, right[a]	Neck
Shoulder girdle, left	Shoulder girdle, right	Upper back
Upper arm, left	Upper arm, right	Lower back

Table 42.2 (continued)

Lower arm, left	Lower arm, right	Chest[a]
		Abdomen[a]
Left lower region (Region 3)	*Right lower region (Region 4)*	
Hip (buttock, trochanter), left	Hip (buttock, trochanter), right	
Upper leg, left	Upper leg, right	
Lower leg, left	Lower leg, right	
2. Symptom severity scale (SSS) score		
Fatigue		
Waking unrefreshed		
Cognitive symptoms		
For each of the three symptoms above, indicate the level of severity over the past week using the following scale:		
0 = No problem		
1 = Slight or mild problems, generally mild or intermittent		
2 = Moderate, considerable problems, often present and/or at a moderate level		
3 = Severe: Pervasive, continuous, life-disturbing problems		
The symptom severity scale (SSS) score: It is the sum of the severity scores of the three symptoms (fatigue, waking unrefreshed, and cognitive symptoms) (0–9) plus the sum (0–3) of the number of the following symptoms the patient has been bothered by that occurred during the previous 6 months:		
1. Headaches (0–1) 2. Pain or cramps in lower abdomen (0–1) 3. And depression (0–1)		
The final symptom severity score is between 0 and 12		
The fibromyalgia severity (FS) scale is the sum of the WPI and SSS		

[a] Not included in generalized pain definition

Table 42.3 AAPT diagnostic criteria for fibromyalgia [10]

Dimension 1 Core diagnostic criteria[a]	1. MSP defined as six or more pain sites from a total of nine possible sites (see Fig. 42.2) 2. Moderate to severe sleep problems OR fatigue 3. MSP plus fatigue or sleep problems must have been present for at least 3 months
Dimension 2 Common features	1. Tenderness—generalized sensitivity of soft tissues and muscles to pressure that would not normally be expected to cause pain 2. Dys-cognition—Presented as difficulties concentrating, forgetfulness, and disorganized or slow thinking 3. Musculoskeletal stiffness—may have a similar pattern to that of inflammatory arthritis, though it is not responsive to corticosteroids 4. Environmental sensitivity or hypervigilance, reflecting central sensitization (e.g., intolerance to bright lights, loud noises, perfumes and cold)
Dimension 3 Common medical and psychiatric comorbidities	• Somatic pain disorders: Irritable bowel syndrome, chronic pelvic pain, interstitial cystitis, chronic head and orofacial conditions (e.g., temporomandibular disorder, otologic symptoms, chronic headaches, and migraine disorder) • Psychiatric conditions: Major mood disorders, anxiety disorders, substance abuse disorder • Sleep disorders: Obstructive and central sleep apnea and restless leg syndrome • Rheumatic conditions, both inflammatory and degenerative • Joint hypermobility • Rhinitis and urticaria • Obesity
Dimension 4 Neurobiological, psychosocial, and functional consequences	• Functional disability • High financial costs including work disability and high health care costs • High mortality, suicide and associations with cancer and cardiovascular disease
Dimension 5 Putative neurobiological and psychosocial mechanisms, risk factors, and protective factors	• Associations: Irritable bowel disorders and other functional bowel disorders, genital urinary disorders, regional pain syndromes • Risk factors: Family history, genetic and environmental factors such as early lifetimes adverse events, infections (EBV, Lyme disease), trauma, and deployment to war • Common comorbidity in other rheumatic conditions: Osteoarthritis, rheumatic arthritis, and lupus

[a] The presence of another pain disorder or related symptoms *does not rule out* a diagnosis of FM. However, a clinical assessment is recommended to evaluate for any condition that could fully account for the patient's symptoms or contribute to the severity of the symptoms

Finally, the 2016 revision aims to combine the ACR 2010 “physician” based criteria with the 2011 modified “patient” criteria into a single set of criteria with two methods of administration that can be used by physicians or patients [14]. This change was made because of the research and comparative analysis of patient and physician assessments in the ACR 2010 study, which indicated a high level of agreement.

The AAPT (ACTTION-APS Pain Taxonomy) Criteria

The AAPT criteria was designed by the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION) public–private partnership with the US Food and Drug Administration (FDA) and the American Pain Society (APS), in order to develop a diagnostic system that would be clinically useful and consistent across chronic pain disorders.

The Fibromyalgia Working Group, which consisted of clinicians and researchers with expertise in FM, aimed to apply the multidimensional diagnostic framework adopted by AAPT to FM, in order to accurately identify the syndrome in clinical practice.

The following criteria exhibit a new approach by defining core criteria, mandatory for a diagnosis, and other “dimensions” which include associated symptoms and signs, comorbidities, and impact on function. Therefore, these criteria allow the physician to focus on a limited number of core symptoms for diagnosis, while other associated symptoms and signs, included in dimension two, can influence by confirming the diagnosis (Table 42.3) [10].

Widespread pain is the core criteria, which all patients should meet. According to the AAPT criteria, FM pain is defined by the ACR 2010/2016 criteria, which focus on the number of body sites with pain, in contrast to the 1990 ACR criteria definition of CWP, which requires a specific anatomical distribution.

Multisite pain (MSP) is defined as the reporting of ≥6 pain sites using a 9-point body manikin (Fig. 42.2). Dimension 2 includes symptoms which are commonly reported by FM patients—fatigue and sleep problems. Arnold et al. [10] identified along with chronic pain, fatigue, and sleep problems as the two principal associated symptoms, proposing a reduction in the number of non-pain symptoms included in diagnostic criteria, as it reduces the complexity of the FM diagnosis and made easier in the use of daily clinical practice.

The other dimensions encompass common medical comorbidities (dimension 3), neurobiological, psychosocial, and functional consequences (dimension 4) and putative neurobiological and psychosocial mechanisms, risk factors, and protective factors (dimension 5) [5]. However, a comparison of the different criteria conducted by Salafi et al. [11]

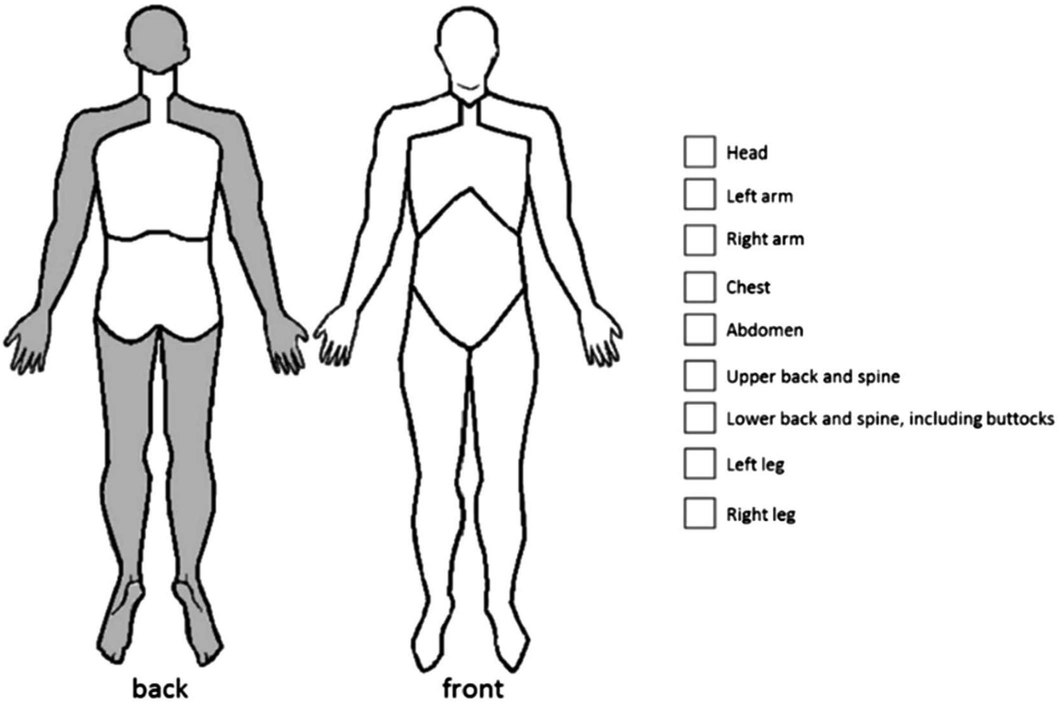

Fig. 42.2 Nine-point body manikin

found that the AAPT criteria had the worst performance with a sensitivity of 73.8% compared to 79.8% and 78% for the ACR 2011 criteria and ACR 2016 criteria, respectively .

Nevertheless, the AAPT taxonomy details a new approach by defining core criteria with other associated symptoms, signs, comorbidities, and its impact on the function of other dimensions [10].

Although tremendous research and test validations had been completed over recent decades, further investigation achieving deeper insight will need to be completed in order to further assess the prevalence and characteristics of chronic pain and in FM within clinical settings.

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IgG4-Related Disease

43

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Abstract

IgG4-related disease (IgG4-RD) is one of the newest autoimmune diseases. The disease causes pseudo-tumoral lesions damaging tissues in multiple organs. Its prevalence and incidence are low, and many conditions can mimic IgG4-RD. Since there is no specific test or feature to make a strong diagnosis, two sets of diagnostic criteria have been developed: The Comprehensive Diagnostic Criteria and the International Consensus on Pathology Criteria. They are based on typical organ involvement, bloodwork, and pathology. Relapses are frequent, and organ involvement can lead to permanent damage. Treatment of IgG4-RD is based on glucocorticoids and steroid-sparing agents.

Keywords

IgG4-related disease · Diagnosis · Autoimmunity · Fibrosis · Criteria

Introduction

IgG4-related disease (IgG4-RD) is a rare, multi-organ, autoimmune fibro-inflammatory disorder characterized by the formation of fibrotic lesions causing organ dysfunction. It was first described in 2001 in type 1 autoimmune pancreatitis (AIP) patients with extrapancreatic lesions and elevated serum IgG4. In 2003, the term IgG4-RD was created encompassing different fibrotic conditions including type 1 AIP, idiopathic retroperitoneal fibrosis, or Mikulicz disease among others [1, 2].

The pathophysiology of IgG4-RD has only been partially clarified. It is thought to be based on interactions between the adaptive and innate immune systems triggered by different antigens [3]. These interactions involve T and B lymphocyte responses. The B cell response, enhanced by T follicular helper lymphocytes, leads to the production of oligoclonal pre-B cells (plasmablasts) and memory B cells, producing IgG4 and IgE. Activated B cells lead to the production of clonally expanded CD4$^+$ cytotoxic T lymphocytes (CTLs) by activated CD4$^+$ T cells. CTLs produce different cytokines damaging the organ tissues and activating M2 macrophages. They also promote fibroblast activation and tissue fibrosis. Currently, IgG4-RD is considered by some authors as a variable-vessel vasculitis. Key presenting characteristics involve organ enlargement mimicking a tumor, often presenting as a systemic disease [4]. Multiple conditions can mimic IgG4-RD including malignancy, infection, and other rheumatological disorders. Therefore, performing an extensive differential diagnosis and establishing a solid diagnosis are capital in managing IgG4-RD.

Epidemiology

The knowledge on IgG4-RD epidemiology is partial only. Older studies from Japan estimated a prevalence of 2.2 cases per 100,000 persons and an incidence of 3.1 per

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100,000 persons. A recent claims-based study in the USA found an incidence of 1.39 per 100,000 person-years and a prevalence of 5.3 per 100,000 persons for 2019 [5]. These rates were comparable to those of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis or systemic sclerosis. Interestingly, the increasing incidence found from 2015 (0.78 per 100,000 person-years) likely reflects a growing awareness about IgG4-RD among physicians. A review including different large IgG4-RD cohorts from multiple countries (America, Europe, and Japan) showed that IgG-4 RD patients were middle aged at diagnosis (50–70 years old) and were predominantly male (1.6–4.1) [6]. The features of the disease could additionally be subject to geographic variability.

Clinical Manifestations

Patients may experience subclinical symptoms for extended durations of time before detection and diagnosis of the disease given its insidious presentation. The presence of allergic features including asthma or eczema can be found in one-third of patients. IgG4-RD can affect most organs, with more than half of patients presenting with multi-organ involvement.

The summary of the potential clinical presentations and manifestations is provided in Table 43.1. Some of the manifestations tend to appear in certain patients simultaneously or progress over time. To simplify and pool these complex presentations, a series of IgG4-RD phenotypes were developed based on a large multinational cohort [7]:

- Pancreato-hepatobiliary disease (31% of the cohort): more common in males, Caucasian ethnicity, elevated serum IgG4 levels, and a quicker time to diagnosis due to complications.
- Retroperitoneal fibrosis and/or aortitis (24% of the cohort): more likely to be male, Caucasian, with minimally elevated to normal serum IgG4 levels.
- Head and neck-limited disease (24% of the cohort): more likely to be female and Asian, elevated serum IgG4.
- Classic Mikulicz syndrome and systemic disease (22% of the cohort): male, Caucasian, with the highest serum IgG4 levels.

Table 43.1 Clinical manifestations of IgG4-RD

Organ and clinical presentations	Clinical manifestations
Salivary glands (parotid, sublingual, submaxillary, Mikulicz disease, Kuttner's pseudotumor) and lacrimal glands	Gland and eyelid swelling, sicca syndrome, visual abnormalities secondary to nerve compression
Ear, nose, and throat	Chronic sinusitis and otitis including headache, nasal crusting, runny nose, hearing impairment
Eyes and orbits (orbit pseudotumor, scleritis, uveitis)	Sicca syndrome, headache, visual impairment
Hypophysis	Diabetes insipidus, hypopituitarism, headache
Central nervous system (hypertrophic pachymeningitis, inflammatory pseudotumor)	Headache, dizziness, deafness, cranial nerve palsy due to compression
Peripheral nervous system (encasement of peripheral nerves)	Compression neuropathy
Thyroid (Riedel's thyroiditis, fibrosing Hashimoto's thyroiditis)	Local pain, dysphagia, shortness of breath due to compression, and hypothyroidism
Lymph nodes	Localized pain or adjacent organ dysfunction due to compression
Breast (tumors or sclerosing mastitis)	Local pain, breast swelling
Lungs and airways (interstitial lung disease, lung nodules, pleural effusion)	Dyspnea, cough
Mediastinum (fibrosing mediastinitis)	Dyspnea, cough, superior vena cava syndrome
Heart (coronary arteries, aorta root, pericardium)	Chest pain, coronary ischemia, acute aortic syndrome, pericarditis
Aorta and great vessels	Pain in the setting of an acute aortic syndrome (dissection, aneurysm), intermittent claudication, edema
Biliary tree and gallbladder	Jaundice, right upper quadrant pain, cirrhosis
Liver (autoimmune hepatitis-like, intrahepatic pseudotumor)	Jaundice, right upper quadrant pain, cirrhosis
Pancreas (AIP1)	Jaundice, endocrine and exocrine pancreatic insufficiency, diarrhea, malabsorption, abdominal pain
Retroperitoneum (retroperitoneal fibrosis, periaortitis)	Chronic back pain, edema, renal dysfunction due to ureteral obstruction, thromboembolic disease, intermittent claudication
Mesentery (mesenteritis, abdominal masses)	Abdominal pain, intestinal obstruction
Gastrointestinal tract (ulcers, polyps, mucosal abnormalities)	Esophageal pain, dysphagia
Kidney (interstitial nephritis, renal mass)	Renal insufficiency, lumbar pain
Prostate and testes	Urinary tract infection symptoms, swelling, scrotal edema, and pain
Skin (cutaneous plasmacytosis, psoriasiform lesions, maculopapular exudative lesions)	Skin lesions
Bone	Local pain due to erosion of the bone

The most frequently involved organs or areas were: pancreato-hepatobiliary (48%), salivary gland (38%), lacrimal gland (26%), retroperitoneum (16%), renal (16%), pulmonary (14%), aorta (10.3%), orbit (7%), and extraocular muscles (4%).

Investigative Findings

Serologic Findings

There are no specific laboratory markers for IgG4-RD. Although serum IgG4 elevations were initially considered as a crucial feature, subsequent studies have demonstrated two problems. First, up to 50% of patients with biopsy-proven IgG4-RD may have normal serum IgG4 levels, especially in non-Asian populations. Second, a multiethnic study from the USA exploring the diagnostic utility of serum IgG4 found a negative predictive value of 96% and a positive predictive value of 34% [8]. Overall, normal levels of serum IgG4 do not exclude IgG4-RD in certain populations, and elevated levels of serum IgG4 do not exclude any mimicker. Finally, serum IgG4 levels partially correlate with IgG4-RD activity and can be used as a biomarker. Plasmablast and CD4$^+$ CTL populations have a good correlation with disease activity but are mainly used for research purposes. The presence of eosinophilia, elevation of IgE, and hypocomplementemia might be present in a fraction of patients. They have been linked to disease activity and to a higher likelihood of flaring [9].

Additionally, several inconsistent findings have been reported including serum C-reactive protein elevation, presence of antinuclear antibodies, hypergammaglobulinemia, or abnormalities in the setting of IgG4-RD organ involvement (increase of creatinine or liver function tests) [10].

Radiographic Findings

There is no imaging test able to establish a definite diagnosis for IgG4-RD, but typical findings are considered supportive for the diagnosis. Imaging, including ultrasound, computed tomography, magnetic resonance imaging, cholangiography, and positron emission tomography can be useful in IgG4-RD to identify tissues amenable to biopsy, assess disease activity and damage [11]. These tests should be indicated depending on the involved organs.

Pathological Findings

The typical pathology findings in IgG4-RD include:

- Lymphoplasmacytic infiltrates: dense infiltrates especially present in the early and active stages of the disease. Predominance of oligoclonal CD4$^+$ T lymphocytes followed by B cells and plasma cells. Occasionally forming germinal centers. There is some macrophage infiltration as well.
- Storiform fibrosis: cart-wheeled collagen bundles developing around fibroblasts.
- Obliterative phlebitis: lymphoplasmacytic infiltrate involving the wall of veins.
- Phlebitis: without obliteration of the lumen.
- Arteritis: not necrotizing, rarer.
- Eosinophilia: moderate to mild tissue infiltration by eosinophils.
- IgG4$^+$ plasma cells: immunostaining showing increased numbers of IgG4$^+$ plasma cells or an elevated IgG4/IgG plasma cell ratio.

The presence of necrosis, microabscesses, giant cells, neutrophil infiltrates, or malignant cells is not typical of IgG4-RD and would point toward other etiologies [12].

Diagnostic Criteria

There are two sets of diagnostic criteria for IgG4-RD, both published in 2012: the Comprehensive Diagnostic Criteria (CDC) [13], and the International Consensus Statement on Pathology Criteria (ICSPC) [12] (Table 43.2).

The CDC are based on a consensus of Japanese experts. They consider the involvement of typical organs, serum IgG4 levels, and IgG4$^+$ plasma cell counts in the pathology exam [12]. Patients are given three diagnostic categories depending on the presence of the different criterion: definitive, probable, or possible. The threshold levels for serum IgG4 and IgG4$^+$ plasma cell counts were made arbitrarily. One of the key points using the CDC is that a possible diagnosis of IgG4-RD can be made only with typical organ involvement and elevated serum IgG4. These general criteria demonstrated a sensitivity of 83–70% for Mikulicz disease and 87–85% for IgG4-related kidney disease [14]. There is no other formal validation of the CDC. Additionally, they were deemed as not useful for some manifestations including type I AIP and in situations where obtaining a tissue sample might be challenging. Therefore, a set of organ-specific criteria were developed for type I AIP, sclerosing cholangitis, IgG4-related kidney disease, IgG-related respiratory disease, and IgG4-related ophthalmic disease. These additional criteria are based on extra criterions including imaging features and other clinical features [13].

The ICSPC are based on an international consensus. In the appropriate clinical setting, pathological findings are

Table 43.2 Diagnostic criteria for IgG4-RD

Criterion	Diagnostic categories	Special considerations
Comprehensive diagnostic criteria [13]		
A. Organ enlargement, mass or nodular lesions, or organ dysfunction B. Serum IgG4 > 135 mg/dl C. Histopathologic examination with: 1. Marked lymphocyte and plasmacyte infiltration and fibrosis 2. Infiltration of IgG4+ plasma cells (ratio of IgG4+/IgG+ plasma cell ratio >40% and >10 IgG4+ plasma cells/HPF)	1. Definite diagnosis: A + B + C 2. Probable diagnosis: A + C 3. Possible diagnosis: A + B	– If organ-specific criteria for IgG4-related AIP, IgG4-related Mikulicz's disease, or IgG4-related kidney disease are met (probable or possible cases), diagnosis is definite IgG4-RD
International consensus statement on pathology criteria [12]		
Clinical presentation suggestive of IgG4-RD and pathology exam with: A. Histology: Presence of dense lymphoplasmacytic infiltrate, and/or storiform fibrosis, and/or obliterative phlebitis B. Immunostaining: Presence in biopsy immunostaining of infiltration by IgG4+ plasma cells fulfilling minimum counts established by organ (10–200 cells/HPF) and IgG4+/IgG+ plasma cell ratio >40%	1. Highly suggestive: ≥2 histological findings of criterion A + criterion B 2. Probable diagnosis: ≥1 histological findings of criterion A + presence of IgG4+ plasma cells not meeting criterion B specifications 3. Insufficient: Not meeting diagnostic categories 1 or 2	– In lacrimal glands, diagnosis can be made only with one histologic feature (usually lymphoplasmacytic infiltrate) – Probable diagnosis confirmation requires serum IgG4 > 135 mg/dl and/or involvement of another typical IgG4-RD organ demonstrated either through radiological or pathological evidence – Insufficient diagnosis might be due to issues with the pathology sample processing or advanced fibrotic states

HPF high power field, *IgG4-RD* IgG4-related disease, *AIP* autoimmune pancreatitis

divided into two categories. First, and most importantly, the typical pathology findings (lymphoplasmacytic infiltrates, storiform fibrosis, and obliterative phlebitis). Second, the IgG4$^+$ plasma cell counts, which are arbitrarily set for each organ, along with an IgG4$^+$/IgG plasma cell ratio ≥0.4. Three diagnostic categories are possible including definite, possible, and insufficient. Patients with not high enough IgG4 counts can obtain a possible diagnosis with other typical organs involved or elevated serum IgG4. Again, there is no formal validation for these diagnostic criteria.

There has been a longstanding debate on which diagnostic criteria are to be used. It is the authors' expert opinion that fulfilling the ICSPC is preferable. Multiple mimicking conditions are among the differential diagnosis in IgG4-RD, and among those, cancer. It has been reported that patients with IgG4-RD have elevated rates of cancer (pancreas, lymphoma) especially during the first years after the diagnosis. Remarkably, most of these patients lacked pathology samples. An accurate early diagnosis can change management and prognosis. Two other consensus support diagnosing IgG4-RD with pathology exams. The 2015 international consensus on IgG4-RD management strongly recommended diagnostic confirmation by biopsy for the exclusion of malignancies and other IgG4-RD mimics [15]. The 2019 American College of Rheumatology/European League Against Rheumatology (ACR/EULAR) classification criteria give the biopsy results a heavy weight (although neither histology, nor serum IgG4 levels are needed to meet the criteria) [16]. Furthermore, they highlight the importance of ruling out other conditions that can be mistaken for IgG4-RD. These classification criteria are not intended for diagnosis but can be usefully applied to navigate through the different diagnostic options and to support a diagnosis of IgG4-RD (sensitivity 82%, specificity 98%).

Prognosis

IgG4-RD patients have a 2.5-fold increased mortality versus controls [5]. This mortality is not completely understood, but long-term complications including organ damage, side effects from immunosuppression, or malignancy (controversial) can justify this finding.

Treatment

Treatment options for IgG4-RD have evolved along time, despite the best evidence being limited to several small clinical trials and retrospective series. The classical management is based on the use of glucocorticoids (GC) [15]. Very occasionally, adjuvant surgery or stenting can be indicated. IgG4-RD characteristically responds to GC, but relapses can occur in more than half of patients. Maintenance treatment with GC has been trialed, reducing flares. Lately, steroid-sparing agents have been shown to be effective for induction treatment in IgG4-RD, and to decrease the number of flares (e.g., mofetil mycophenolate, leflunomide, rituximab). Unfortunately, access to some treatments is geographically restricted. This fact, along with regional drug preferences, has led to a wider use of GC alone in Asia, opposed to the mixed use of GC and steroid-sparing agents in America and Europe [17]. There are ongoing clinical trials with novel therapeutic agents including elotuzumab, rizalbrutinib, zanibrutinib, inebilizumab, and belimumab. The results of these studies may modify the management of IgG4-RD in the coming years.

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ASIA Syndrome

44

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Abstract

Autoimmune/Inflammatory syndromes induced by adjuvants (ASIA) encompasses a cluster of related immune-mediated diseases, which develop among genetically prone individuals as a result to an adjuvant agent exposure. These conditions share several clinical aspects with the possible appearance of autoantibodies and of full-blown autoimmune diseases, trend to improve once the inciting agent is removed. According to a report on the international ASIA syndrome registry, the most frequent symptoms are fatigue, arthralgia, and myalgias. These individuals also exhibit a significant decline in their capacity to participate in activities they could engage in before their illness, including work, education, social interactions, and personal pursuits. In recent years, an increasing body of evidence in the medical literature has shed light on the ASIA syndrome, revealing novel aspects that enhance our understanding of this puzzling condition. Furthermore, additional elements are being proposed as part of new diagnostic criteria for ASIA, including dysregulated non-classical autoantibodies targeting coupled receptors of G protein of the autonomic nervous system and the presence of small fiber neuropathy. Regrettably, there have been no randomized clinical trials conducted to address the management of ASIA, and there is a lack of established guidelines. Nevertheless, drawing from our own clinical experiences, several therapeutic considerations can be proposed.

Keywords

ASIA syndrome · Autoimmune/inflammatory syndrome induced by adjuvants · Adjuvants · Vaccine · Autoantibodies · Silicone · Autoimmunity

For many years, it has been known that autoimmune diseases can be triggered by different factors in a susceptible patient [1]. Nevertheless, it was not until 2011 that certain identified trigger molecules were associated with four specific conditions (silicosis, the Gulf War syndrome, the macrophagic myofasciitis syndrome, and post-vaccination phenomena). In these four conditions, a different specific trigger or adjuvant (*adjuvare* in Latin, meaning aid) that helped ignite the immune system was found as a common denominator. This association of an adjuvant and an autoimmune-related disease was called "Autoimmune/ Autoinflammatory Syndrome Induced by Adjuvants" or ASIA syndrome [2]. After the first description of the syndrome by our group (YS), many other authors have described cases in which patients began to experience a wide range of symptoms after exposition to silicone, polypropylene, silica, mercury, mineral oil, aluminum hydroxide used in vaccines, and other agents [3].

Some studies have found that these conditions do not appear in all individuals but in those predisposed by genetic means, such as mutations in HLA-DRB1 and PTPN22 genes, which are well known to contribute to the susceptibility of autoimmune diseases [4]. Other HLA genes that have been associated are DQB1, B57/B35, A2/A24, DR52, DR17, and DQ2 [5]. Nevertheless, not everyone suspected of having ASIA undergoes genetic studies; therefore, we have not found other genetic risk factors in these patients.

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When a predisposed patient is exposed to these adjuvants, different mechanisms from the immune system start the autoimmunity process. Some tools are antibody production due to continuous exposition to these antigens, the moving of antigens to lymph nodes where T-cells recognize them, as well as the increase of danger signals in the injection site and the interaction with Toll-like receptors (TLR) and activation of the inflammasome. Not only the innate immune system is involved in the pathogenesis of ASIA, but the adaptive immune system participates in the enhancement of CD4+ T cells and Th2 cytokine production [6].

Some specific antibodies have recently been linked to autonomic nervous system symptoms. These antibodies are directed against the coupled receptors of G protein (GPCRs) in the autonomic nervous system, like anti-B1 adrenergic, anti-endothelin type A, or anti-angiotensin ll type 1. GPCRs regulate the body's autonomic responses, such as heart rate and blood pressure. The presence of autoantibodies targeting these GPCRs indicate an immunological dysfunction in regulating autonomic functions. These autoantibodies can contribute to the pathogenesis of the condition by interfering with the normal operation of GPCRs, thus affecting autonomic regulation. This finding is supported by the fact that antibodies and symptoms disappear after the withdrawal of the adjuvant [3].

Clinical Spectrum

The first symptoms described in patients with ASIA were broad and not specific, such as myalgias, arthralgias, chronic fatigue, and sleep disturbances [7]. Nevertheless, in recent years, more evidence has been published in which adjuvants induce specific autoimmune diseases such as Sjögren syndrome, systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, and others [3]. Also, Jara et al. [8] reported a review of ASIA with severe presentations. They found more than 300 cases with significant organ involvement like transverse myelitis, heart failure, hemolytic anemia, and even one patient with fatal results.

According to a report on the international ASIA syndrome registry, the most frequent symptoms are fatigue, arthralgia, and myalgias [9]; this finding is similar to the reported by Colaris et al. [7], who described the symptoms of two cohorts separated by 30 years. Table 44.1 summarizes the most frequent symptoms reported in various studies. Interestingly, fatigue, anxiety, and depression have been described following small fiber neuropathy (SFN) diagnosis. SFN is presented in patients with damage to the structure of myelinated A-delta and non-myelinated C-fibers, particularly at the distal nerve terminations, thus giving us a more reliable basis for the pathogenesis and presentation of ASIA.

Table 44.1 Clinical manifestations in ASIA (*n*: 582)

Symptom	Frequency	Percentage
Fatigue	482	82.81
Arthralgias/arthritis	444	76.28
Myalgia	431	74.05
Headache	241	41.40
Cognitive impairment (memory loss)	222	38.14
Fever	217	37.28
Sicca syndrome	200	34.36
Raynaud's phenomenon	136	23.36

Taken from references [3, 7, 9]

Laboratory Markers

Due to the multiple and varied manifestations of ASIA syndrome, the findings in laboratory studies will depend on the primary manifestation. Nevertheless, it is currently known that patients may, in some cases, have antibodies against the adjuvant, or as previously mentioned, GPCR antibodies may be found [3]. It has also been proven that antiphospholipid antibodies appear in mice after immunization with an adjuvant; this association was observed 5 months after the application of Freund's adjuvant and compared to control groups by Katzav et al. [10]

Alijotas et al. [11] reported their findings of a cohort of 185 patients with a history of ASIA after injections of biomaterials like hyaluronic acid, acrylamides, or methacrylate. They found an increase in acute phase reactants such as c-reactive protein (CRP) in almost 100% of their patients. Also, they found antinuclear antibodies (ANAs) in 60% of patients and abnormal complement C4 levels in 26.7% of patients. Positive ANAs have been reported to be associated with ASIA in patients with silicone breast implants previously; as Boer et al. reported, these antibodies remained positive after the explanation of the silicone implants [12].

Asia Syndrome Diagnostic Criteria

The disease spectrum varies between men and women, mainly depending on the adjuvants they were exposed to. In 2011, Shoenfeld et al. introduced a set of major and minor criteria intended to assist in diagnosing ASIA syndrome, as outlined in Table 44.2 [13].

One of the initial indicators of ASIA is the onset of myalgias, arthralgias, or arthritis, impacting over 90% of patients. Most individuals meet the 2016 criteria for fibromyalgia. Morning stiffness, lasting more than an hour, is a common occurrence. In some instances, patients may present with symmetric polyarthritis resembling rheumatoid arthritis.

Generally, individuals diagnosed with ASIA typically endure chronic fatigue. They often wake up already feeling

Table 44.2 Criteria for the diagnosis of autoimmune/inflammatory syndrome induced by adjuvants (ASIA). Patients are considered to have ASIA when either two major or one major and two minor criteria are present

Major criteria
Exposure to an external stimulus (implants such as silicone and mesh are classic adjuvants) prior to clinical manifestations
The appearance of "typical" clinical manifestations such as:
• Chronic fatigue, unrefreshing sleep or sleep disturbances
• Myalgia, myositis or muscle weakness
• Arthralgia and/or arthritis
• Cognitive impairment, memory loss
• Pyrexia
• Sicca (dry mouth, dry eyes)
• Neurological manifestations (especially associated with demyelination)
Removal of inciting agent induces improvement
Typical biopsy of involved organs
Minor criteria
The appearance of autoantibodies or antibodies directed at the suspected adjuvant
Other clinical manifestations (i.e., irritable bowel syndrome, Raynaud's phenomenon)
Specific HLA associations (i.e., HLA-DRB1, HLA DQB1)
Involvement of an autoimmune disease (i.e., multiple sclerosis, rheumatoid arthritis, Sjögren syndrome, systemic sclerosis

The diagnosis can be established by meeting either two major criteria or one major criterion along with at least two minor criteria

tired, and this fatigue persists despite rest. These individuals also exhibit a significant decline in their capacity to participate in activities they could engage in before their illness, including work, education, social interactions, and personal pursuits. Sleep disturbances, such as difficulties falling or staying asleep, are commonly noted among ASIA patients. These sleep problems are closely tied to heightened levels of fatigue. Moreover, cognitive impairment symptoms are likely linked to poor sleep quality, resulting in memory lapses, absentmindedness, difficulties finding words, and challenges with sustained attention. Severe neurological symptoms are present in 30–40% of patients, including ischemic cerebral disease, multiple sclerosis-like syndrome, or amyotrophic lateral sclerosis-like disease [14].

New-onset Raynaud's phenomenon can also be present, while in other instances, pain and paresthesia point toward a diagnosis of SFN. Furthermore, most patients report pyrexia and night sweats, while others report dry eyes and a dry mouth. Gastrointestinal problems are prevalent, including abdominal pain and altered bowel movements akin to irritable bowel syndrome. Around 20–40% of patients experience ill-defined skin rashes, severe pruritus, or alopecia [14, 15].

The histopathological findings linked to ASIA syndrome exhibit variability depending on the affected organ or specific condition. Proposed features encompass the development of granulomas—aggregates of immune cells such as macrophages and lymphocytes—signifying inflammatory reactions across diverse tissues. Notably, biopsies have reported the presence of macrophages with aluminum nanocrystals in their cytoplasm and even lymph nodes containing scattered silicone particles. Furthermore, there are signs of increased proliferation of lymphoid tissue, autoimmune-related changes characterized by the deposition of immune complexes, and alterations in connective tissue. These changes could potentially lead to fibrosis, significant structural modifications, and even the development of malignancy [12, 14, 15].

In recent years, growing evidence of the ASIA syndrome has been reported in the literature, bringing to light new elements that strengthen this enigmatic condition. Moreover, additional players are being proposed as part of new criteria for ASIA syndrome, including dysregulated non-classical autoantibodies targeting GPCRs of the autonomic nervous system and SFN [16]. These factors may provide partial explanations for the development of "dysautonomia," a commonly reported panoply of symptoms among ASIA patients [17].

Can the Disease Be Predicted and Prevented?

Defining a Population at Risk for Asia Syndrome

Currently, it's not feasible to foresee who will develop ASIA syndrome. However, it does manifest in genetically predisposed individuals, including those carrying genes like HLA-DRB1, HLA-DQB1, and PTPN22, as previously mentioned. Clustering of autoimmune diseases in families is well recognized, supporting a common genetic susceptibility. In such cases, the adjuvant triggers an exaggerated immune system response, ultimately resulting in the development of ASIA syndrome. Furthermore, if the patient possesses a family or personal background of autoimmune and/or inflammatory disorders, the likelihood of developing ASIA syndrome might be higher [18]. It is already known that individuals diagnosed as having any autoimmune disease are at a higher risk of developing another autoimmune disorder. Likewise, subjects with prior documented autoimmune reaction to an adjuvant (vaccination, implants, etc.), the prevention of co-adjuvant effect though a new stimulant exposure should be advised.

Allergies are reported in 50–80% of the patients. In most instances, these allergies are pre-existent. In many cases, however, patients report that allergic symptoms had vanished prior to the adjuvant stimulus but returned thereafter [14, 18]. Importantly, a significant number of ASIA patients have a humoral immune-deficiency and/or a vitamin D deficiency. These two factors also increase the likelihood of develop an autoimmune inflammatory disease in susceptible patients [3].

Therapy

Regrettably, there have been no randomized clinical trials conducted to address the management of ASIA, and there is a lack of established guidelines. Nevertheless, drawing from our own clinical experiences, several therapeutic considerations can be proposed.

First and foremost, it is crucial to address or manage factors that can trigger immune activation. Patients should prioritize quitting smoking, maintaining a normal body weight, engaging in regular physical exercise, and adopting a healthy and balanced diet [3, 13]. Furthermore, it is essential to identify and rectify any nutritional deficiencies, with a particular focus on vitamin D due to its role in immune system regulation. Assorted studies have indicated that vitamin D supplementation can also help alleviate chronic widespread pain and fatigue among ASIA patients [19]. Moreover, individuals who suffer from ASIA syndrome resulting from implants such as silicone or polypropylene meshes may potentially find relief through implant removal. Unfortunately, whether symptoms will improve after explanation is not definitively predictable, as it greatly hinges on factors like the type of adjuvant, the duration of exposure, and the likelihood that it has disseminated to remote sites [20].

There is currently no cure for ASIA, but symptom reduction is possible through therapy. Diverse drugs have been recommended including minocycline, doxycycline, hydroxychloroquine, or corticosteroids to mitigate inflammation. In severe cases, the consideration of intravenous immunoglobulin (IVIg) at a dosage of 2 mg/kg may be warranted. Finally, a comprehensive approach involving pharmaceutical interventions, cognitive-behavioral therapy, and exercise-based treatments should be explored [8, 14, 20].

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Immune Adverse Effects Induced by Checkpoint Inhibitors

45

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Abstract

The blocking of specific control points through the use of monoclonal antibodies against CTLA-4 and PD-1/PD-L1, known as immune checkpoint inhibitors (ICI), has not only allowed better control of various neoplasias but has also brought with it the appearance of a series of immune-mediated phenomena that affect practically any organ and that suppose a challenge for the clinician. We describe here the primary clinical syndromes induced by ICI, emphasizing rheumatic and systemic syndromes.

Keywords

Immune checkpoint inhibitors · Immune-related adverse events · Rheumatic immune-related adverse events

Introduction

Immune checkpoint inhibitors (ICI) are a novel class of cancer immunotherapy that has revolutionized the treatment landscape. They work by blocking certain immune checkpoints, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or the programmed cell death-(ligand) 1 (PD-1/PD-L1), which cancer cells exploit to evade the immune system (Table 45.1).

Table 45.1 Checkpoints inhibitors

CTLA-4	PD-1	PD-L1
Ipilimumab	Nivolumab	Avelumab
Tremelimumab	Pembrolizumab	Atezolizumab
	Cepelimumab	Durvalumab
	Pidilizumab	

CTLA-4 cytotoxic T-lymphocyte antigen 4, *PD-1* programmed cell death 1, *PD-L1* programmed cell death ligand 1

By inhibiting these checkpoints, these drugs unleash the body's immune response, enabling it to recognize and attack cancer cells more effectively. ICI have demonstrated remarkable success used alone or in combination with another ICI or cytotoxic chemotherapy across various cancer types, including melanoma, renal cell carcinoma, colon-rectal cancer, urothelial cancer, hepatocellular carcinoma, among others, leading to durable and often long-lasting responses in a subset of patients. However, their effectiveness can vary and may be associated with immune-related adverse effects (irAEs).

Precise mechanisms are not well-described. Some proposed mechanisms underlie irAEs such as (1) autoimmunity activation, (2) loss of tolerance, (3) cytokine release, (4) tissue-specific antigen expression, (5) dysregulated immune cell activation, and (6) the presence of some genetic factors [1].

Clinical Manifestations

The irAEs involve the immune system attacking healthy tissues, resulting in several clinical syndromes. These autoimmune complications stem from the intricate balance between immune activation and regulation disrupted by ICI [1, 2].

Potentially, irAEs can affect any single organ or system but usually involve the endocrine system, skin, gastrointestinal, lungs, and musculoskeletal systems (Fig. 45.1). In this chapter, emphasis will be made on the most frequent rheumatic and systemic irAEs caused by ICI.

Some factors are related to a higher risk of irAEs, including previous underlying autoimmune disease, combined therapies (CTLA-4 plus PD-1 or PD-L1), and a history of previous irAEs [3].

In a recent systematic review, the most common irAEs reported were hypothyroidism (5%), pneumonitis (2%), colitis (0.7%), and hypophysitis (0.3%) [4].

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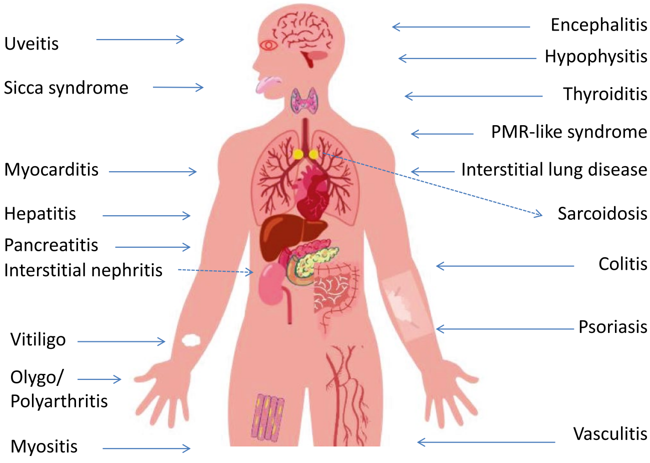

Fig. 45.1 Main irAEs induced by ICI

Endocrine irAEs are common and might affect any system in many ways, including thyroiditis, adrenal insufficiency, autoimmune diabetes mellitus, and hyperparathyroidism [1, 3].

Dermatological involvement is also common in the form of vitiligo, followed by others such as alopecia areata or universalis, dermatitis herpetiform, panniculitis, psoriasis, pyoderma gangrenosum, and bullous pemphigoid, among others. The clinical presentations vary from local to diffuse distributions, including flexural, inverse, and erythrodermic variants.

Gastrointestinal reactions included diarrhea, colitis, autoimmune hepatitis, lymphocytic gastritis, and pancreatitis. There is a lot of similarity between ICI-induced colitis and inflammatory bowel disease. The distribution of colitis has been reported to involve the descending colon more often than other parts.

Neurological manifestations are diverse and include central nervous system (CNS) and peripheral nervous system (PNS) complications. Among CNS, encephalitis, meningitis, and hypophysitis are the most common. Other irAEs include CNS demyelination lesions with transverse myelitis, multiple sclerosis-like, and neuromyelitis optica. PNS includes radiculopathies and neuropathies. ICI-induced myasthenia gravis sometimes overlaps with myositis [1, 5].

Pulmonary irAEs, mainly pneumonitis (including sarcoidosis and organizing inflammatory pneumonitis), are, on occasion, severe and life-threatening.

Hematological complications include aplastic anemia, autoimmune cytopenias, and, less commonly, hemophagocytic lymphohistiocytosis.

Acute interstitial nephritis is the major kidney-related adverse effect of ICI. Other manifestations, such as glomerulonephritis, electrolyte abnormalities, and renal tubular acidosis, have been described.

Ocular manifestations are diverse and include anterior uveitis, serous retinal detachment or panuveitis resembling Vogt–Koyanagi–Harada syndrome, papillitis, diplopia or other ocular motility defects, episcleritis, and conjunctivitis [1].

Rheumatic and Systemic Syndromes

There is an increase in rheumatic and systemic irAEs reports, due to increased usage of ICI and a better recognition of these new associations. Patients experiencing rheumatic complications or other irAEs are more likely to have a partial or complete response to their underlying malignancy [6]. In this chapter, emphasis will be made on the most frequent rheumatic and systemic irAEs caused by ICI.

Most irAEs consisted of organ-specific autoimmune diseases and, less frequently, systemic and rheumatic diseases. The rheumatic irAEs include arthralgias/myalgias, arthritis, a clinical syndrome resembling polymyalgia rheumatica (PMR-like), myositis, Sicca/Sjögren syndrome (SS), vasculitis, and sarcoidosis, among others. Each of these rheumatic toxicities has its prevalence and chronology of onset after treatment with ICI. Rheumatic irAEs tended to occur within the first 8 months of immunotherapy [7]. The main characteristics of rheumatic irAEs are summarized in Table 45.2.

Arthritis

Musculoskeletal irAEs are not uncommon and are increasingly recognized, including ICI-induced arthritis, of which arthralgia is the most common, with a prevalence ranging from 5% to 20% [10].

Four patterns are well described, including rheumatoid arthritis (RA)-like, a clinical syndrome resembling polymyalgia rheumatica (PMR-like), psoriatic arthritis (PsA)-like (Fig. 45.2), and oligo-monoarthritis (e.g., reactive arthritis-like disease or large joint oligoarthritis with or without axial disease), among others. Some patients develop noninflammatory arthritis, usually transient and responding well to symptomatic treatment. It is also important to note that patients with previous osteoarthritis may develop inflammatory joint pain some weeks after starting ICI therapy.

The clinical course in ICI-induced arthritis is variable, including a self-limited flare, an intermittent course with flares and remission, and a chronic persistent pattern, as occurs in inflammatory arthritis. Some patients had a chronic course after ICI cessation [11].

PMR is increasingly recognized as one of the most common inflammatory rheumatic irAEs. A reasonable question is whether these cases of irAE represent a disorder identical to the idiopathic form of the disease or, rather, a new entity. The diagnosis of PMR relies on the presence of a compatible clinical picture (i.e., stiffness and pain in the shoulders and hip girdle) combined with the detection of inflammatory markers and glucocorticoid response.

Some irAE-PMR cases contained atypical features, including synovitis, positive serology for rheumatoid factor (RF) and/or anti-cyclic citrullinated protein antibodies, and

Table 45.2 Main rheumatic irAEs induced by ICI

Category	Articular					Muscular		Systemic	Vasculitic	Granulomatous
		Inflammatory arthritis								
Subtypes	Arthralgia	RA-like	PsA-like	Others[a]	PMR-like	Myalgias	Myositis	Sicca/Sjögren's syndrome	Vasculitis	Sarcoidosis
Prevalence	1–43%	1–7%			<2%	2–21%	<1%	3–24%	<1%	0.2%
Onset	Weeks–months	<3–4 months			10 days–16 months	Weeks–months	<1 month	<3 months	1 week–18 months	3–36 weeks
Main characteristics	Inflammatory and non-inflammatory	Symmetric polyarthritis	Oligo-, mono-, or polyarthritis		Stiffness and pain in the shoulders and hip girdle Atypical manifestations may occur	Usually precedes muscle weakness	Proximal muscle weakness, myalgias MG, bulbar involvement, myocarditis High mortality (21%) Myocarditis (52%)	More frequent in men, higher mean age, highest prevalence of xerostomia, a predominant immunonegative serological profile, and higher ESSDAI	Male predominance Mainly LVV and vasculitis of the central or peripheral nervous system	Asymptomatic (incidental), cutaneous or systemic (mainly pulmonary)
Diagnosis approach	–	High ESR/CRP, most seronegative (ANA, RF, anti-CCP), HLA-B27 negative X-ray, ultrasound, MRI, CT			High ESR/CRP Ultrasound, Whole-body ^{18}F-FDG PET/CT	–	High CK, aldolase, hs-cTnT Most seronegative (MSA, MAAs, anti-AChR, anti-MuSK) EMG, MRI (fasciitis), biopsy	Most seronegative (anti-Ro/SSA, La/SSB, RF). Labial gland Biopsy	High ESR/CRP, Whole-body ^{18}F-FDG PET-CT, CT, angiogram, MRI, EMG, biopsy	CT Biopsy
ICI type most commonly associated	PD-1/PD-L1	PD-1/PD-L1			PD-1/PD-L1	–	PD-1	PD-1/PD-L1	CTLA-4	CTLA-4 PD-1/PD-L1

Adapted from [5, 8, 9]

Sicca syndrome, vasculitis, and sarcoidosis are usually associated with malignant melanoma

ANA antinuclear antibodies, *anti-CCP* anti-cyclic citrullinated proteins antibodies, *anti-AChR* anti-acetylcholine receptor antibodies, *anti-MuSK* anti-muscle-specific kinase antibodies; *CK* creatine kinase; *CTLA-4* cytotoxic T-lymphocyte antigen 4; *CRP* C-reactive protein; *EMG* Electromyography; *ESR* erythrocyte sedimentation rate; *ESSDAI* EULAR Sjögren's syndrome disease activity index, *hs-cTnT* high-sensitive cardiac troponin T; *ICI* immune checkpoint inhibitors, *LVV* Large vessel vasculitis; *MG* Myasthenia gravis; *MAAs* myositis-associated autoantibodies; *MRI* magnetic resonance imaging; *MSA* myositis-specific antibodies; *PD-1* programmed cell death 1; *PD-L1* programmed cell death ligand 1; *PET-CT* positron emission tomography scan, *PMR* polymyalgia rheumatica; *PsA* psoriatic arthritis; *RA* Rheumatoid arthritis; *RF* rheumatoid factor

[a] Spondyloarthropathy, reactive arthritis-like, remitting seronegative symmetrical synovitis with pitting edema syndrome (RS3PE), tenosynovitis, Jaccoud arthropathy, enthesitis, undifferentiated arthritis, exacerbation of osteoarthritis, calcium pyrophosphate dihydrate crystal deposition disease and gout

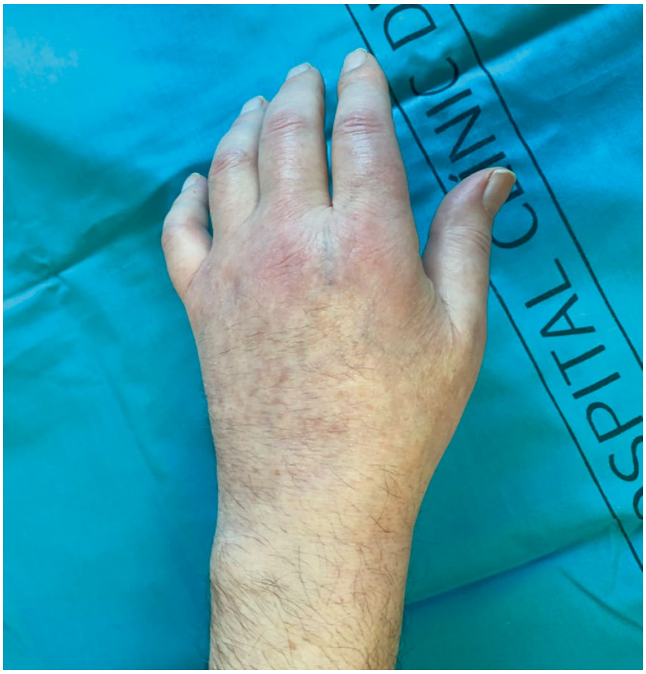

Fig. 45.2 Arthritis induced by ICP. Note signs of dactylitis, in second, third, and fourth fingers of left hand

more severe presentations than generally encountered in classical PMR [12].

Patients receiving ICIs should be asked about joint symptoms and referred as soon as possible to a rheumatologist if arthritis is suspected for diagnostic workup, which includes serum parameters (inflammatory markers and autoantibodies) and imaging studies (Ultrasound [US], ^{18F}FDG-PET/CT, MRI).

Imaging techniques are helpful monitoring tools for diagnosing and following patients with ICI-induced arthritis. US findings disclosed significant inflammatory changes, for instance, in patients with RA-like and PMR-like disease, as in chronic inflammatory arthropathies. These findings have implications for the diagnosis, treatment, and prognosis, requiring, in some cases, DMARD therapies. Careful analysis of ^{18F}FDG-PET/CT, focusing on detecting signs of rheumatic irAEs, could potentially help oncologists during follow-up to request a prompt assessment by rheumatologists. The utility of MRI seems to be for unresolved issues, suspected early erosive disease, or muscle or myofascial involvement [10].

Myositis

Myositis secondary to checkpoint inhibitor use is a rare but potentially severe complication described in cancer immunotherapy. The frequency of myalgias is 4% in randomized controlled trials, and they are often classified as mild, whereas myositis has been reported in 0.6% of individuals receiving ICIs [13].

Clinical manifestations include muscle weakness (often affecting the proximal muscles), myalgia, limb-girdle weakness, ptosis, or oculomotor weakness. Muscle weakness is often preceded by myalgia and appears shortly after treatment initiation. Notably, cases of ICI-associated myositis with concomitant myasthenia gravis, myocarditis, or both have been reported, often with poor outcomes [13]. Some well-characterized inflammatory myopathies (dermatomyositis, polymyositis, and anti-synthetase syndrome) have been described.

Previous data suggest that PD-1 and PD-L1 inhibitors-associated myopathy may present with various clinical manifestations and degrees of severity, including myasthenia gravis, necrotizing myopathy, and cardiomyopathy. A characteristic clinic-pathological pattern, including a myasthenia gravis-like syndrome plus myositis, has been described in patients receiving PD-1 and PD-L1 inhibitors. A significant component of macrophages and T-cells resembling granulomas (pseudo granulomatous necrotic infiltrate) seems to be the pathological hallmark of this syndrome [14].

Diagnosing myositis typically involves assessing clinical symptoms, elevated muscle enzyme levels (e.g., creatine kinase, aldolase), electromyography (showing a myopathic pattern), and muscle biopsy to confirm the inflammatory changes in muscle tissue. Cardiac biopsy is the gold standard for diagnosing myocarditis. Early recognition and prompt intervention are crucial to managing myositis in patients receiving ICI, as it can lead to significant morbidity and necessitate treatment interruption.

Sicca Syndrome

Oral and ocular dryness are reported as irAE in 5.3% of patients with cancer treated with immunotherapies included in RCTs. Sicca symptoms were frequently observed in patients with other rheumatic irAE, including symmetric polyarthritis and arthralgias/myalgias [7]. About 60% of patients with ICI-associated Sicca syndrome meet the classification criteria for SS. Patients with SS triggered by ICI display a specific profile different from that reported in idiopathic primary SS, including more frequent occurrence in men, a higher mean age, the highest prevalence of xerostomia, a predominant immunonegative serological profile, and a notable development of organ-specific autoimmune involvement (mainly cutaneous and articular). The predominant seronegative immunological pattern is similar to that reported for other irAEs related to cancer immunotherapies. A predominant T-lymphocytic infiltrate, with a slight majority of $CD4^+$ over $CD8^+$ T cells and few B cells, has been described in patients under ICI treatment [15].

The diagnosis of Sicca syndrome includes a combination of clinical evaluation and specialized tests, including Schirmer's test for tear production, salivary gland scintigraphy to assess saliva secretion, the presence of autoantibodies (ANA, anti-Ro/SSA, anti-La/SSB antibodies, and RF), and pathological study of minor salivary glands.

Vasculitis

Several types of vasculitis have been reported as irAEs and range from single organ involvement to small, medium, and large vessel involvement. Among the rheumatic irAEs, vasculitis is less commonly reported and tends to occur later than other irAEs. The disease pattern can be heterogeneous, and thus, a high suspicion of these conditions is required.

Giant cell arteritis is the most frequently reported systemic vasculitis, with reported cases of Schönlein–Henoch purpura, cryoglobulinemic vasculitis, pulmonary vasculitis, eosinophilic granulomatosis with polyangiitis, periaortitis, isolated aortitis, and primary angiitis of the central nervous system.

Accurate diagnosis relies on clinical presentation, serological markers (ANCA, cryoglobulins), and vascular involvement should be assessed using imaging and, whenever possible, with histopathological study of the involved organ such as the skin, nerve or temporal artery biopsy. Given the overlapping presentation with other autoimmune diseases and infections, it is mandatory to exclude other etiologies and thus may require extensive investigations [16].

Sarcoidosis and Others

Granulomatous disorders, including sarcoidosis secondary to ICI therapy, are an uncommon but noteworthy complication. The lymph nodes, lungs, and skin are the primary affected organs, although other systemic manifestations have also been reported. Clinical manifestations often encompass a range of non-specific symptoms, such as fatigue, cough, dyspnea, and skin lesions, which can mimic cancer progression.

The diagnosis involves a comprehensive assessment, including imaging studies like chest X-rays and thoracic CT, pulmonary function tests, and biopsy of affected tissues. Histopathological confirmation of non-caseating granulomas in the absence of cancer progression and other causes (primarily infectious) of granulomatosis is highly recommended for diagnosis [5]. Less frequent irAEs secondary to ICI include lupus (systemic, subacute cutaneous, lupus nephritis, lupus-like), fasciitis with myositis syndrome, systemic sclerosis, and antiphospholipid syndrome (APS).

Differential Diagnosis

The differential diagnosis of immunological adverse events secondary to checkpoint inhibitor use involves considering a wide range of potential causes. These symptoms can overlap with various conditions, including underlying autoimmune diseases, infections, and other adverse effects of cancer therapies. Discriminating between these possibilities requires a comprehensive assessment of clinical history, physical examination, laboratory tests, and imaging studies. A wide list of mimickers of irAEs is described in Table 45.3. Differentiating immune-related adverse events from preexisting autoimmune conditions demands a thorough understanding of the patient's medical history and appropriate serologic markers.

Moreover, ruling out infections is critical, often necessitating targeted cultures and serologic tests. The intricate interplay between immune checkpoint inhibitors and the body's immune responses makes accurate diagnosis challenging yet essential for tailored management strategies. Close collaboration between oncologists, rheumatologists, and other specialists is crucial to achieve a precise differential diagnosis and ensure appropriate interventions for patients experiencing these complications [8, 17].

Table 45.3 Mimickers of rheumatic and systemic syndromes induced by ICI

Inflammatory disorders
• Crystalline arthritis (gout or pseudogout)
• Paraneoplastic arthritis
• Sarcoid arthropathy
Mechanical/degenerative musculoskeletal disorders
– Osteoarthritis/activated osteoarthritis
– Tendinitis/traumatic tendinitis/tenosynovitis
Other chronic pain disorders
– Fibromyalgia
– Complex regional pain syndrome
Infectious diseases
– Post-viral arthritis/arthralgia
– Bacterial arthritis
– Mycobacterial arthritis
– Lyme arthritis
Bone diseases
– Tumor-induced osteomalacia
– Metastasis (in proximity to joints)
– Hypertrophic osteoarthropathy (Marie–Bamberger disease)
Neuropathies
– Chemotherapy induced neuropathy
– Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes syndrome (POEMS syndrome)
– Parsonage Turner syndrome
Metabolic and endocrinologic
– Arthralgia associated to endocrine disease (e.g., hypothyroidism, diabetes mellitus)
– Hypophysitis
Cutaneous syndromes
– Eosinophilic fasciitis
– Paraneoplastic vasculitis
– Sweet syndrome
– Erythromelalgia

New Criteria in Progress

Until today, there are no well-established classification criteria for irAEs. Currently, a group of experts from ACR/EULAR is working on definitions and preliminary phases using well-known methodologies previously used for other autoimmune diseases such as systemic lupus erythematosus or APS. As mentioned, differential diagnosis is complex in patients with active neoplastic diseases under ICI or other agents.

Clinical Approach and Management

A multidisciplinary approach is needed for the treatment of patients with ICI. It is crucial to balance the risk/benefit of keeping ICI therapy according to disease prognosis, previous response to other therapeutic schemes, and severity of irAEs (from grade 1 to grade 4 according to National Cancer Institute definitions) [18]. Usually, mild to moderate irAEs are treated with glucocorticoids, and sometimes hold ICI therapy is needed. For grades 3–4, permanent discontinuation is needed, especially for severe complications such as myocarditis, severe cytopenias, uncontrolled colitis, DRESS syndrome, severe hepatitis, and pneumonitis requiring admission, among others.

In some cases of grade 4 endocrinopathies, ICI should be continued if it is controlled by hormone replacement. In patients with persistent symptoms and partial or lack of response to oral glucocorticoids (i.e., arthritis, colitis, myositis), some additional treatment is needed, including azathioprine, methotrexate, or even biological therapies (e.g., anti-TNF or anti-IL-6). For cases of severe myositis, pulses of methylprednisolone, intravenous immunoglobulins, or abatacept are recommended [19].

Conclusions

The increasing use of ICI has also increased the appearance and identification of various immune-mediated complications that are challenging for the clinician. The prevalence of irAEs secondary to ICI can vary widely depending on the specific cancer type, the checkpoint inhibitor used, and the population being studied. Timely diagnosis of irAEs secondary to ICI is crucial as early recognition and intervention can mitigate potentially severe complications and optimize patient outcomes.

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Part V

Endocrine and Reproductive Autoimmune Diseases

46

Hashimoto's Thyroiditis

Ifigenia Kostoglou-Athanassiou and Yehuda Shoenfeld

Abstract

Autoimmune Hashimoto's thyroiditis is an organ-specific autoimmune disorder. It affects the thyroid gland and is characterized by the presence of antibodies to thyroid proteins, namely, thyroid peroxidase and thyroglobulin antibodies, thyroid tissue invasion by lymphocytes and reduced echogenicity of the thyroid on ultrasonography. The presence of Hashimoto's thyroiditis may be associated with normal thyroid function, hypothyroidism and rarely hyperthyroidism. Hashimoto's thyroiditis with normal thyroid function may progress to subclinical hypothyroidism or overt hypothyroidism. Hypothyroidism is treated by the administration of thyroxine usually for life.

Keywords

Autoimmune Hashimoto's thyroiditis · Thyroid peroxidase antibodies · Thyroglobulin antibodies · Hypothyroidism · Subclinical hypothyroidism · Thyroxine

Disease Description

Autoimmune Hashimoto's thyroiditis is an organ-specific autoimmune disorder. It affects the thyroid gland and is characterized by the presence of antibodies to thyroid proteins, namely, thyroid peroxidase and thyroglobulin antibodies and thyroid tissue invasion by lymphocytes. The presence of Hashimoto's thyroiditis may be associated with normal thyroid function, hypothyroidism and rarely hyperthyroidism. Hashimoto's thyroiditis with normal thyroid function may progress to subclinical hypothyroidism or overt hypothyroidism.

Risk factors for the development of Hashimoto's thyroiditis are genetic and environmental. Genetic factors are HLA-DR4, CD40, CTLA-4 and PTP-N22 and genetic factors related to thyroglobulin gene and TSH receptor gene. Environmental factors include the presence of iodine excess in the environment, infectious agents such as hepatitis C virus and the SARS-CoV-2 virus, selenium deficiency, drugs such as amiodarone, interferon-a, highly active antiretroviral therapy and immune checkpoint inhibitors. Smoking is a protective factor. Female sex is also a risk factor for Hashimoto's thyroiditis.

Presently there are experimental efforts to pause or reverse the autoimmune process which leads to Hashimoto's thyroiditis and may progress to the destruction of the thyroid gland, which have not yet been applied therapeutically. If a patient has subclinical hypothyroidism in the presence of Hashimoto's thyroiditis, thyroxine is necessary. Hypothyroidism is treated by the administration of thyroxine usually for life.

History

Autoimmune Hashimoto's thyroiditis is a chronic autoimmune thyroid disorder characterized by the presence of goiter in many cases, hypothyroidism in several cases and the presence of antibodies to thyroid antigens in the blood [1–3]. It is a frequent disorder and the most frequent cause of hypothyroidism.

Hashimoto in 1912 described the disease in four women who had surgery for goiter and in whom lymphocytic infiltration of the thyroid was observed in the thyroid biopsy [4]. More than 70 years ago, Noel Rose injected thyroglobulin in rabbits and observed the development of antibodies against thyroglobulin and thyroid inflammation, thus discovering autoimmune thyroiditis [5]. In 1956, Roitt et al. discovered the presence of antithyroid antibodies in cases of autoim-

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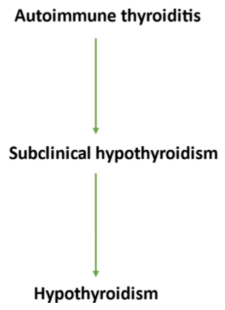

Fig. 46.1 The progression of autoimmune thyroiditis

mune thyroiditis [6]. Chronic autoimmune thyroiditis presents mainly with two types of clinical presentation, one presenting with goiter and another presenting with thyroid atrophy and degeneration. Silent and postpartum thyroiditis are two forms of chronic autoimmune thyroiditis.

The development of methods for the detection of antithyroid antibodies and measurement of TSH has led to the diagnosis of cases of chronic autoimmune thyroiditis in patients with normal thyroid function, who in the course of the disease develop subclinical or clinical hypothyroidism (Fig. 46.1).

Prevalence and Incidence

Autoimmune thyroiditis affects 5–7 times more women than men, usually middle aged or older as well as younger patients and children. The prevalence of the disease differs depending on three diagnostic criteria, namely (a) the presence of thyroid tissue lymphocytic infiltration (b) the detection of antithyroid antibodies, and (c) the presence of increased TSH levels.

Foci of thyroiditis 1–10/cm^2 of thyroid tissue in biopsies were observed in 40–45% in females and 20% in males. If the diagnostic limit increases to >40/cm^2 foci of thyroiditis, the prevalence is lower, i.e., 5–15% in females and 1–5% in males. The incidence of Hashimoto thyroiditis is 1.3% in children 11–18 years. In adult women, the incidence is 3.5 per 1000 per year and in men 0.8 per 1000 per year. Although in a worldwide basis the commonest cause of hypothyroidism remains iodine deficiency, in areas of adequate iodine intake the commonest cause of hypothyroidism is Hashimoto's thyroiditis with a worldwide estimated annual incidence of 0.3–1.5 cases per 1000.

Pathogenesis

Hashimoto's thyroiditis is an autoimmune disorder which may be due to an abnormal immune reaction. T lymphocytes are involved in the pathogenesis of Hashimoto's thyroiditis and polyclonal antibodies are produced targeting thyroid cells. The autoimmune disorder is initiated by the activation of CD4 T helper lymphocytes specific for thyroid antigens [7]. In the literature, two hypotheses have been developed for the activation of these cells.

According to the first hypothesis, an infection with a virus or a bacterium which has a protein similar to a thyroid protein may induce the activation of T lymphocytes specific for the thyroid, a theory known as theory of molecular mimicry. According to an alternative hypothesis, epithelial thyroid cells present their intracellular proteins to helper T lymphocytes. Following their activation autoreactive CD4 T lymphocytes may stimulate autoreactive B lymphocytes which produce thyroid antibodies. Activated T lymphocytes induce the concentration of cytotoxic CD8 T lymphocytes and B lymphocytes within the thyroid [8]. The direct destruction by T lymphocytes of thyroid cells is believed to be the main mechanism responsible for the development of hypothyroidism. Thyroid antibodies may also play a pathogenetic role. Increased apoptosis may be involved in the mechanism of thyroid cell destruction in Hashimoto's thyroiditis.

Etiology

Various genetic, epigenetic and environmental factors predispose to the development of chronic autoimmune thyroiditis (Fig. 46.2).

Genetic Factors

Various genetic factors have been recognized. The genes encoding the major histocompatibility complex HLA have been implicated in the pathogenesis of Hashimoto's thyroiditis [9]. The presence of Tyr26, Gln70, Lys71 and Arg74 in the HLA-DRβ1 molecule may cause structural changes in pocket 4 of the molecule, thereby influencing binding of thyroid-derived pathogenic peptides thus predisposing to the development of autoimmune thyroiditis. The presence of Tyr30 in pocket 6 of the HLA-DR molecule may also cause structural changes and predispose to the development of autoimmune thyroiditis [10]. Cytotoxic T lymphocyte associated antigen-4 (CTLA-4) [11] and protein tyrosine phosphatase-22 (PTPN22) [12] are major negative regulators of T-cell-mediated immune function. Polymorphisms of the CTLA-4 and PTPN22 genes have been linked with Hashimoto's thyroiditis. However, the mechanisms through which susceptibility to thyroid autoimmunity is induced are yet unknown. The presence of A-1623 A/G single-nucleotide polymorphism at the thyroglobulin promoter may influence binding of nuclear transcription factors such as interferon regulatory factor-1 protein [13]. Increased production of interferon-γ in a viral infection may increase expression of

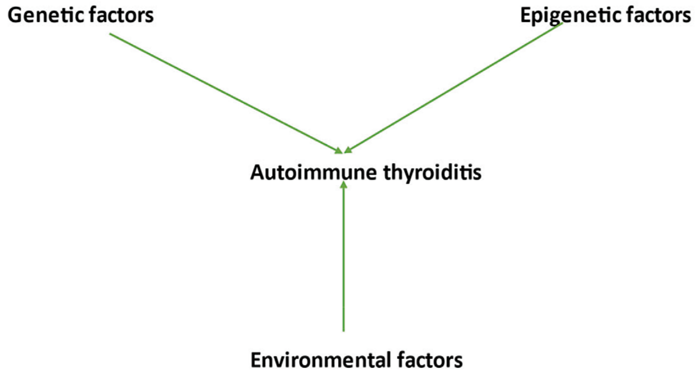

Fig. 46.2 Factors contributing to the development of autoimmune Hashimoto's thyroiditis

thyroglobulin and lead to activation of T-cell response, thus leading to the development of thyroid autoimmunity. A polymorphism in the CD40 gene has significant effects on CD40 on antigen-presenting cells, including B lymphocytes, influencing B-cell proliferation, antibody secretion and generation of memory cells, thus leading to thyroid autoimmunity.

Environmental Factors

Infections and iodine are environmental factors which may predispose to the development of Hashimoto's thyroiditis. Infectious agents, such hepatitis C or the SARS-CoV-2 viruses, may induce autoimmunity by molecular mimicry, tissue infection or destruction [14]. An increased prevalence of antithyroid antibodies has been observed in residents in areas with iodine excess [15]. Salt iodination may induce the development of thyroid autoimmunity.

Selenium

Selenium deficiency may be related to the development of thyroid autoimmunity [16].

Estrogens

Autoimmune Hashimoto's thyroiditis has a higher prevalence in female patients [1]. There is a sex dimorphism in the immune response [17]. Female patients have a stronger immune response. The cost is an increased susceptibility to autoimmune diseases.

Drugs

Amiodarone. Amiodarone has a high iodine content and affects thyroid function. It may induce autoimmune thyroiditis, hypothyroidism or hyperthyroidism.

Highly active antiretroviral therapy. Highly active antiretroviral therapy (HAART) for the treatment of HIV patients is related to a higher incidence of subclinical hypothyroidism.

Interferon-a. Interferon-α is used for the treatment of hepatitis C and is associated with the development of autoimmune thyroiditis, hypothyroidism and destructive thyroiditis.

Immune checkpoint inhibitors. Immune check point inhibitors are a major step forward in the treatment of cancer. However, their administration is related to the development of autoimmune thyroiditis and autoimmune hypophysitis.

Clinical Presentation

The most frequent clinical findings in chronic autoimmune thyroiditis are goiter and hypothyroidism or both.

As far as goiter is concerned, the thyroid is homogenously enlarged, has a semi-hard consistency and its surface is uneven. In some cases, the enlargement is uneven, and it may appear as a nodule or multinodular goiter. Lymphoma is observed in 0.1% of patients with chronic autoimmune thyroiditis and it is 80 times more frequent than expected.

As far as hypothyroidism is concerned, patients with positive antithyroid antibodies are euthyroid in 50–75%, 25–50% have subclinical hypothyroidism and 5–10% have clinical hypothyroidism. Patients with positive antithyroid antibodies and normal or increased TSH and normal T_4 may present with hypothyroidism in the course of the disease. In clinical hypothyroidism, signs and symptoms of hypothyroidism are observed, and the diagnosis is easy (Table 46.1). In subclinical hypothyroidism, however, there are no symptoms, although it has been reported that in comparison with euthyroid people there may be symptoms, such as cold intolerance, dry skin, fatigue, depression, disorders of cognition and atypical response to psychiatric intervention. Additionally, Canaris et al. [19] comparing the symptoms of hypothyroidism to those of subclinical hypothyroidism found that the symptoms of patients with subclinical hypothyroidism were intermediate as compared to those of clinical hypothyroidism and those of euthyroid individuals.

Table 46.1 Percentage of symptoms and signs in clinical hypothyroidism (modified) [18]

Symptoms	(%)	Signs	(%)
Fatigue	88	Dry coarse skin	90
Cold intolerance	84	Voice hoarseness	87
Dry skin	77	Facial periorbital edema	76
Voice hoarseness	74	Slowed movements	73
Decreased hearing	40	Mental impairment	54
Sleepiness	68	Bradycardia <60/min	10
Impaired memory	66	Bradycardia>60/min	90
Weight gain	72		
Paresthesia	56		
Constipation	52		
Hair loss	41		

Interestingly, some patients on thyroxine treatment may present with persistent symptoms which may be due to the autoimmune process itself.

Diagnosis

For the diagnosis of chronic autoimmune thyroiditis history, clinical presentation and laboratory findings are used.

History and Clinical Presentation

The presence of other members of the family with chronic autoimmune thyroiditis will be sought, as the disease may present in families. If there is goiter, the time of presentation will be sought, the size and its change in the course of time, as in thyroiditis the thyroid is gradually enlarged in the course of time. The presence of pressure symptoms will be sought in the trachea and the esophagus. The presence of symptoms of hypothyroidism will also be sought.

Palpation of the thyroid gland will be performed to identify the consistency of the gland, which may be semi-hard and its surface uneven. The findings of hypothyroidism will also be investigated. It should be noted that a rare clinical finding is encephalopathy, Hashimoto’s encephalopathy, which regresses either without treatment or by the administration of corticosteroids.

Laboratory Findings

Laboratory examination includes biochemical examinations and ultrasonography.

Biochemical examinations. The main characteristic of chronic autoimmune thyroiditis is the presence of thyroid antibodies. The titer of thyroid peroxidase antibodies is increased in 95% approximately and those of thyroglobulin antibodies in 60–80% of the cases. Titers of thyroid antibodies are higher in the fibrotic disease than in that with goiter. In micronodular goiter, the prevalence of Hashimoto’s thyroiditis is increased. In chronic autoimmune thyroiditis, both thyroid peroxidase and thyroglobulin antibodies are usually present; however, only one type may be observed. Thyroglobulin antibodies represent an earlier innate type of immune response, whereas thyroid peroxidase a later adaptive immune response, a sort of immune escalation [3].

Table 46.2 Proposed diagnostic criteria of Hashimoto’s thyroiditis as discussed by Caturegli et al. [3] with their sensitivity

Reduced echogenicity on ultrasonogram	18–77%
Thyroid peroxidase antibodies	95%
Thyroglobulin antibodies	60–80%

Ultrasonography. The ultrasonogram may be diagnostic of chronic autoimmune thyroiditis. It reveals increased size of the gland with diffuse hypoechoic areas in 18–77% of cases. Foci of mixed or increased echogenicity may be found in the gland parenchyma, which may be a sign of fibrosis.

Diagnostic Criteria

As diagnostic criteria reduced echogenicity of thyroid on ultrasonography, the presence in serum of thyroid peroxidase antibodies and thyroglobulin antibodies is proposed (Table 46.2). The presence of thyroid peroxidase antibodies is now considered the best serological marker to establish the diagnosis of Hashimoto’s thyroiditis. Thyroid peroxidase antibodies have a higher sensitivity and specificity as they are present in 95% of patients and rarely in healthy controls. Thyroglobulin antibodies have a lower sensitivity as they are present in 60–80% of patients and in a larger number of healthy controls.

Silent and Postpartum Thyroiditis

Silent and postpartum thyroiditis are thought to be manifestations of chronic autoimmune thyroiditis.

Silent Thyroiditis

Silent thyroiditis is a frequent cause of hyperthyroidism. It is called silent as it does not manifest with pain. If affects equally male and female patients. Hyperthyroidism is mild and there is no history of upper respiratory infection. Hyperthyroidism is due to thyroid hormone release in the blood due to cell lysis. Thyroid hormone levels vary depending on the stage of the disease. The most characteristic finding of silent thyroiditis is decreased ^{131}I uptake. Thyroid peroxidase antibodies are detected in 60% of cases and thyroglobulin antibodies in 25% of cases. Treatment with antithyroid drugs is not considered necessary as hyperthyroidism is not severe and subsequently hypothyroidism ensues. Beta-blockers may be administered. The disease may recur.

Postpartum Thyroiditis

Postpartum thyroiditis is frequent. It appears within the first-year postpartum and affects 5–10% of female patients. The disease may evade diagnosis, as its symptoms may be attributed to postpartum depression. In its classical presentation, it presents with transient hyperthyroidism usually 6 weeks–6 months postpartum, which may not require treatment. Hypothyroidism follows which may recede or may become permanent and is treated with thyroxine. Postpartum thyroiditis is an autoimmune disease. Pregnancy is a period of immunosuppression which is followed by a period of rebound immune activation postpartum. Thus, the titer of thyroid antibodies decreases during pregnancy and may increase in the postpartum period. The presence of thyroid peroxidase antibodies affects pregnancy outcome.

Treatment

Thyroid antibody titers are not an index of thyroid function, and they are not an indication for thyroxine administration, except if there is subclinical or clinical hypothyroidism. Subclinical hypothyroidism should be treated with thyroxine if thyroid antibodies are present. Clinical hypothyroidism should be treated with life-long thyroxine administration. At present, experimental efforts take place to block T-cell activation by thyroglobulin by small molecules, such as cepharanthine, in experimentally induced autoimmune thyroiditis and thus stop the progression of the disease [20]. The administration of selenium and vitamin D may interfere with the progression of autoimmune thyroiditis. Hypothyroidism in chronic autoimmune thyroiditis is not always permanent, and there is a percentage of patients who recover, and thyroxine may be withdrawn.

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Atrophic Autoimmune Thyroiditis

47

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Abstract

Atrophic autoimmune thyroiditis (AAT) is an organ-specific autoimmune disease characterized by thyroid autoantibodies, functional hypothyroidism, and absence of goiter.

Atrophic autoimmune thyroiditis is a rare entity that occurs most frequently between 40 and 60 years of age. Immunogenetic analysis suggests that AAT may differ from Hashimoto's disease. Genetic and environmental factors interact, leading to autoantigens with autoantibody formation. Atrophic autoimmune thyroiditis is a Th2 disease with blocking anti-TSH receptor antibodies. Hashimoto's thyroiditis, primary myxedema, or AAT, and Graves' disease could be different expressions of a similar process. The immune response may include cytotoxic antibodies, stimulatory antibodies, blocking antibodies, or cell-mediated immunity. The clinical presentation varies from asymptomatic AAT to overt hypothyroidism and myxedema. The pathological features are an atrophic thyroid gland with lymphocytic infiltration and fibrous tissue replacing normal thyroid parenchyma. There are no current diagnostic criteria for AAT. We propose the following bases for AAT diagnosis: clinic or subclinical hypothyroidism, positive thyroid stimulation-blocking antibodies, and thyroid ultrasound with diffuse low thyroid echogenicity associated with a reduced thyroid volume. In asymptomatic AAT, preventive thyroid replacement therapy is indicated in patients with elevated basal TSH levels.

Keywords

Atrophic autoimmune thyroiditis · Antithyroid antibodies

Nomenclature

TSHr-Ab	TSH receptor antibodies without definition of assay method or functional properties
TRAB	TSH receptor antibodies detected by binding assay without definition of functional property
TSAb	TSH receptor stimulating antibodies which act as agonists by stimulating thyroid growth and thyroid hormone synthesis
TBAb	TSH receptor-blocking antibodies which act as antagonists, by blocking the action of the TSH
TBII	TSH-binding inhibitory immunoglobulins
TSII	TSH-stimulated cAMP response inhibitory immunoglobulins
TGII	TSH-stimulated cell growth inhibitory immunoglobulins (Nomenclature adapted from Napolitana G, et al. Frontiers in Endocrinology; 2021;12:3)

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Introduction

Atrophic autoimmune thyroiditis (AAT) is an organ-specific autoimmune disease characterized by thyroid autoantibodies, functional hypothyroidism, and absence of goiter. By thyroid ultrasound (US), AAT is defined as a gland with an estimated volume of <4.5 ml (females) and <5.5 ml (males). The scope of thyroid pathology is broad and encompasses developmental, inflammatory/immunological, functional, and neoplastic disorders. In AAT, the factors leading to a histological description of this entity are post-inflammatory pituitary/hypothalamic failure and exogenous thyroid hormone [1]. On the other hand, multiple pieces of evidence do not prove that goiter precedes AAT. However, genetic studies support the concept that AAT is a different entity. Indeed, HLA-DRB1*04 and HLA-DQB1*03 are associated with AAT but not with the goitrous form of chronic autoimmune thyroiditis [2].

The purpose of this chapter is to describe the clinical, imaging, and immunological evidence that allows us to describe AAT as a defined entity. At the same time, to propose classification criteria for AAT.

History

The initial report of autoimmune thyroid disease (AITD) dates to 1912 when Hakira Hashimoto described four women in whom the thyroid gland was enlarged and appeared to have transformed into lymphoid tissue ("struma lymphomatosa") as an organ-specific autoimmune disease with diffuse infiltration of lymphoid cells and parenchymal atrophy. On the other hand, Sir William Withey Gull is credited with the first description of the atrophic form of chronic autoimmune thyroiditis in 1873. There is controversy on whether AAT is considered the end-stage of goitrous disease because little histological progression has been observed inpatients up to 20 years of follow-up [1].

Epidemiology

AITD is the most common of all autoimmune diseases, affecting 1.5% of the population, mainly women; however, AAT is an infrequent condition. AAT is, after ablation, hypothyroidism, the most common cause of thyroid failure in adults, and it usually occurs between the ages of 40 and 60. In Tunisia, AAT was present in 32.2% of a cohort of 1079 patients [3]. In Germany, AITD usually manifests as AAT with functional hypothyroidism affecting older women [4]. The effects of chronic exposure to a mixture of air pollutants on thyroid gland function are not yet sufficiently known. In this regard, a recent study suggests a higher incidence of AAT and Hashimoto's thyroiditis in an urban population, indicating that more research should be carried out [5].

Pathogenesis

The pathogenesis of AAT is not entirely elucidated. As in other forms of AITD, genetic and environmental factors appear to interact, leading to the appearance of autoantigens; furthermore, T lymphocytes are crucial in the pathogenesis of autoimmune thyroiditis. The interplay between the environmental and genetic factors and ncRNAs and microbiome contributes to AITD development. In particular, the authors describe mechanistic models by which SNPs in genes involved in immune regulation and thyroid function, such as CD40, TSHR, FLT3, and PTPN22, underlie AITD predisposition [6, 7] Loss of immunological tolerance to self-antigens is a central mechanism in AITD. Potential major (thyroglobulin, thyroid peroxidase, and thyrotropin receptor [TSHR]) and minor (sodium iodide symporter [NIS], pendrin, and megalin) antigens are found in thyroid tissue [8]. Various autoantibodies against these antigens are found in patients with different AITD [9]. Anti-TSH receptor antibodies (TRAbs) are of relevance in patients with AAT. Early studies found these antibodies present in 20–50% of patients with AAT. In contrast, these antibodies are also found in up to 10% of patients with goitrous thyroiditis and hypothyroidism. From a biological and functional point of view, TRAbs can be classified as stimulatory, blocking, or neutral [9]. TSH receptor-blocking antibodies (TBAbs) have been reported in 25–59% of adult patients with AAT [6, 10]. Initial reports showed that TBAbs are less frequently observed in children. However, a recent Japanese study found that TSAbs are as expected (38.8%) as in adult patients [11]. TBAbs seem to have a pathogenic role in AAT since they inhibit the metabolic pathways activated by TSH and its receptor, inhibiting hormone synthesis [10]. Therefore, decreased hormone production leads to glandular atrophy with the consequent development of clinical hypothyroidism characteristic of AAT [12]. Furthermore, in children, it has been shown that TBAbs correlate with THS levels [13]. AAT with TBAbs may be regarded as the opposite end to that of Graves' disease. Here again, the predominance of humoral immunity may enhance the production of anti-TSH receptor antibodies. Lymphocytic infiltration is a hallmark feature of AITD, with a predominance of autoreactive B cells, cytotoxic T lymphocytes, and CD4$^+$ cells [7]. Activation of CD4$^+$ cells is considered an early event in AITD, leading to thyroid damage and TSAbs production by autoreactive B cells. The interaction of CD4$^+$ cells with thyroid antigen-presenting cells (APC) favors their activation and phenotypic differentiation. Th1, Th2, and Th17 cells destroy thyroid tissue through cytotoxicity mechanisms and cytokines. Proinflammatory

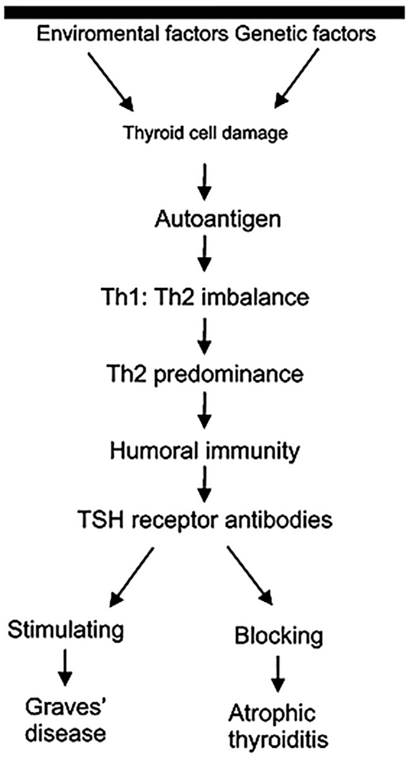

Fig. 47.1 The proposed pathogenic mechanisms of AAT include the interaction between environmental and genetic factors. The consequence is thyroid cell damage with expression of neoantigens and stimulation of immune response, leading to Th2 cytokines production and consequently blocking autoantibody formation. These cytotoxic autoantibodies (anti-TBAb) seem to be responsible for autoimmune thyrocyte depletion. (Adapted from Fountoulakis and Tsatsoulis, ref. [6])

cytokines secreted by these activated cells, such as IL-2, IL-17, INF-γ, and TNF-α, are involved in the effector damage mechanisms in different AITD. Unlike Hashimoto's thyroiditis, AAT is a disease with a predominance of the Th2 response, as in Graves' disease (Fig. 47.1) [3]. The role of Th17 cells is beyond doubt in Hashimoto's thyroiditis but is less compelling in Graves' disease [14]. On the other hand, the study of Treg cells in AITD has shown mixed results. Furthermore, these results seem to be influenced by the effect of the patient's treatment. In any case, the counter-regulatory balance may be insufficient to contain the proinflammatory effects of Th17 cells in AITD patients [14].

Genetic Factors

HLA associations with AAT have been described since the 1970s. Subsequent studies found that HLA-DR3 increased in patients with AAT and HLA-DR5 in patients with goitrous autoimmune (Hashimoto's), compared with controls. These findings stress the immunogenetic heterogeneity between goitrous thyroiditis and AAT. HLA A, B, C, DR, and DQ alloantigens serologically and HLA-DQ by gene analysis were determined in patients with AAT and randomly chosen controls. The genetic susceptibility to AAT was closely associated with HLA-DR5 and DQ7 and was not distinct from goitrous disease. Factors other than genetic ones explain the different immunological and clinical manifestations of chronic lymphocytic thyroiditis.

In contrast, using the same methods, Cho et al. [15] investigated in Korean patients whether the associations between HLA alleles of patients with autoimmune hypothyroidism varied according to the presence or absence of TRBabs. The frequency of HLA-DR8 and HLA-DQB1*0302 was significantly increased in AT patients who were highly positive for TSH-binding inhibitor immunoglobulin compared with controls and those with goitrous autoimmune thyroiditis. This study concluded that TRBabs-positive AAT is immunogenetically different from goitrous autoimmune and TRBabs-negative AAT.

The localization and functional characteristics of the tumor necrosis factor (TNF) beta gene (the short arm of chromosome 6) raise the possibility that it may be involved in the susceptibility to AITD. Chung et al. [16] analyzed the TNF beta gene polymorphism with the restriction enzyme NcoI in Korean AT patients with and without TRBab, goitrous autoimmune thyroiditis, and healthy controls. The frequency of HLA-DR8 antigens was significantly increased in patients with TRBab-positive AAT compared with control subjects. The DR8-positive patients with TRBab-positive AAT had more TNF beta* 1 allele homozygotes than the DR8-negative patients with TBRab-positive AAT and DR8-positive controls. This association may be related to susceptibility markers responsible for producing TRBab in AAT patients. Zantut-Wittmann et al. [4] demonstrated that DRB1*04 and DQB1*03 alleles are associated with AAT only, supporting the concept that genotypic differences exist between goitrous and atrophic forms. In summary, four types of genetic influence have been pointed out in chronic autoimmune thyroid disease: Major histocompatibility complex genes, T-cell immune response genes, other immune-regulatory genes involved in peripheral tolerance (e.g., FOXP3 and CD25), and thyroid-specific genes; these mechanisms participate in many other autoimmune disorders [2].

Immunological Factors

Immunological mechanisms have been sequentially proposed to be responsible for autoimmune thyrocyte depletion in AAT.

Early reports showed that AAT produces antibodies that block the thyroid growth-promoting activity of TSH. The effects of IgG from patients with AAT on cAMP responses and iodine metabolism (post-receptor processes) using cultured thyroid cells were examined. Two thyroid function-blocking antibodies in AAT were found: TSH-binding blocking antibodies and antibodies that block post-receptor processes.

These antibodies might be responsible for thyroid dysfunction in AAT and may induce AAT. The frequency of TSH-binding inhibitory immunoglobulins (TBII), TSH-stimulated cAMP response inhibitory immunoglobulins (TSII), and TSH-stimulated cell growth inhibitory immunoglobulins (TGII) in patients with AAT was higher than in patients with autoimmune goitrous thyroiditis. These antibodies block TSH-induced cAMP production and TSH-induced DNA synthesis and iodine uptake in cultured thyroid cells [17]. Antithyroid stimulation-blocking antibodies are detectable in 46% of AAT patients and almost exclusively in overt hypothyroid patients [8]. Their prevalence is higher in hypothyroid patients with AAT than in Hashimoto's disease, suggesting a role in developing hypothyroidism and AAT [8, 9]. Analysis of cytotoxicity regarding thyroid size showed a higher incidence of cytotoxic antibodies in AAT vs. goitrous disease. The specific lysis in AAT patients was significantly higher than in goitrous patients. The histopathological features of AAT with TBII antibodies were carried out using immunohistochemical procedures. Significant follicular atrophy with epithelial flattening, including decreased positive staining of the follicular epithelial cells for thyroglobulin in AAT, was characteristically observed [18]. These results suggest that the mechanism for developing hypothyroidism in AAT with TBII might suppress thyroid cell function by inhibiting endogenous TSH stimulation by blocking antibodies with subsequent epithelial degenerative destruction [19].

Autoimmune destructive mechanisms, such as antibody-dependent cytotoxicity, K and NK cytotoxicity, T-lymphocyte cytotoxicity, lymphokine cytotoxicity, and apoptosis, have been proposed to be responsible for autoimmune thyrocyte depletion in Hashimoto's thyroiditis and Graves' disease [12]. However, there are scarce studies on AAT. It has been suggested that Hashimoto's thyroiditis, primary myxedema or AAT, and Graves' disease are different expressions of a similar autoimmune process and that the clinical appearance reflects the spectrum of the immune response in the patient. This response may include cytotoxic antibodies, stimulatory antibodies, blocking antibodies, or cell-mediated immunity. Thyrotoxicosis is an expression of the effect of circulating thyroid stimulatory antibodies. Hashimoto's thyroiditis is predominantly the clinical expression of cell-mediated immunity leading to the destruction of thyroid cells, which in its severest form produces thyroid failure and idiopathic myxedema or AAT [20].

Clinical Manifestations

The clinical presentation of AAT varies from asymptomatic AAT to overt hypothyroidism and myxedema. Asymptomatic AAT is characterized by serum antithyroid antibodies in good correlation with thyroid lymphoplasmocytic infiltrations. Asymptomatic AAT affects 5–15% of the general population, especially older women. Patients with asymptomatic AAT have no goiter and are clinically euthyroid. While circulating thyroid hormones are always in the normal range, peak TSH, TRH, and basal TSH values increase in two-thirds of the cases [4]. There is a familial aggregation of asymptomatic AAT and a frequent association with other autoimmune diseases such as Sjogren's syndrome, autoimmune hepatitis, atrophic gastritis, type I diabetes mellitus, adrenal insufficiency, vitiligo, and systemic lupus erythematosus [2]. Development of overt hypothyroidism with classic symptoms/signs (lethargy, constipation, cold intolerance, and myxedematous facies) in these patients is habitual. Occasionally, patients with AAT may present asthenia, diffuse myalgia, notable hair loss, and sinus bradycardia. Young patients with muscular fatigability, myalgia, cramps, or proximal weakness of uncertain origin may have AT, and the evaluation of thyroid function is appropriate [4].

The rare AAT mainly presents as primary myxedema and is discovered less frequently while exploring unclear hypercholesterolemia. It is generally admitted that primary myxedema in adults is the outcome of autoimmune AAT. Other rare manifestations of AAT and associations include myxedema pericarditis, cardiac tamponade, dissecting aneurysm of the aorta, neuropsychological deficits, multiple sclerosis, and myocardial infarction [1, 4]. The differential diagnosis of AAT is shown in Table 47.1.

Table 47.1 Differential diagnosis in AITD

Characteristic	Subclinical autoimmune thyroiditis	Classic Hashimoto's thyroiditis	Atrophic autoimmune thyroiditis
Stage	Early	Advanced	Final
Antithyroid antibodies	Positive	Positive	Positive
Goiter	None or very small	Large	None
Thyroid function	Euthyroid	Euthyroid hypothyroid Destructive thyrotoxicosis	Hypothyroid

Pathological Features

AAT is characterized by an atrophic thyroid gland with lymphocytic infiltration and fibrous tissue replacing normal thyroid parenchyma.

Morphological observations were carried out to investigate the histopathological features of AAT with TBII using additional immunohistochemical procedures. There exist apparent differences between AAT and Hashimoto's thyroiditis. Significant follicular atrophy with epithelial flattening, including decreased positive staining of the follicular epithelial cells for thyroglobulin in AAT, was characteristically observed. These results suggest that the mechanism for developing hypothyroidism in AAT with blocking type-TBII might suppress thyroid cell function by inhibiting endogenous TSH stimulation by the blocking antibody with subsequent epithelial degenerative destruction [12].

Diagnostic Studies

An abnormal thyroid echographic pattern characterized by a diffuse low thyroid echogenicity associated with a reduced thyroid volume was found in 96% of patients with AAT. Of interest, in 18% of patients, the scintiscan was normal. Thyroid echography can be considered the first morphological study in AAT with high specificity and sensitivity. Other studies are necessary to define antibodies' positive and negative predictive value in AAT.

Treatment. In asymptomatic AAT, preventive thyroid replacement therapy is indicated in patients with elevated basal TSH levels. Overt hypothyroidism always requires hormonal substitution [1].

Diagnostic Criteria

There are no current diagnostic criteria for AAT. Therefore, we propose the following bases for AAT diagnosis:

1. Clinic or subclinical hypothyroidism: Absence of thyroid enlargement and clinical picture of overt hypothyroidism or increased TSH and TRH values with low free T4 level without symptoms.
2. Positive thyroid autoantibodies: Positive TSH receptor-blocking antibodies (TBAbs).
3. Thyroid ultrasonographic characteristic: Abnormal thyroid echographic pattern characterized by diffuse-low thyroid echogenicity associated with a reduced thyroid volume.

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Subacute Thyroiditis

48

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Abstract

Subacute thyroiditis (SAT), also known as giant cell thyroiditis, subacute granulomatous thyroiditis, de Quervain's thyroiditis, or pseudogranulomatous thyroiditis, was described for the first time in 1895 by Mygind. It is the most common cause of thyroid pain, although it is a rare cause of thyrotoxicosis. It is a self-limiting inflammatory disorder and can be triggered by many viral infections being recently associated with COVID-19. It presents with an elevation of acute phase reactants as well as an elevation of triiodothyronine (T3) and thyroxine (T4) and a decrease of thyroid-stimulating hormone (TSH). Usually, the autoantibodies are negative. The classical course of the disease includes a stage of hyperthyroidism followed by a stage of hypothyroidism, usually transitory. SAT has a symptomatic treatment and consists of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids when is more symptomatic. Beta-blockers improve symptoms of hyperthyroidism.

Keywords

Subacute thyroiditis · De Quervain's thyroiditis · Thyrotoxicosis · Pseudogranulomatous thyroiditis · Thyroid pain

Epidemiology

Subacute thyroiditis is an infrequent cause of thyrotoxicosis [1]. The total age and sex-adjusted incidence has changed over time; from 8.7 in the 1960s to 3.6/100,000 per year in the 1990s [2], and the rates between genders are different, with more women than men. This disease occurs most often in people 40–50 years old. Despite being present in childhood, while is rare in the elderly. SAT is more frequent in women, with a 6:1 female-to-male gender ratio [3]. A tendency to a seasonal and geographical aggregation of cases has been noted, being more frequent in spring and summer, and so there has been a suggested linkage with certain viruses such as echovirus and coxsackie virus, an association with other viruses such as measles virus, Epstein–Barr virus, and recently H1N1, SARS-CoV2 [4], and dengue virus. It has been reported that at least 20% of the hospitalized patients with COVID-19 had symptoms of SAT [5]. SAT could also be induced by drugs, such as tumor necrosis factor (TNF)-α inhibitors, interferon-α, and lithium treatment.

Pathogenesis

The etiology of SAT is unknown; various mechanisms involving a virus-induced response have been proposed. After a viral infection, an apoptotic response is triggered in the follicular epithelium, which releases preformed thyroglobulin that were stored in the thyroid gland. However, there is not enough evidence to establish a cause-effect pattern.

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Genetics plays an important role, and it is recognized that there is a higher incidence of SAT in those with the histocompatibility antigen (HLA) HLA-Bw35, HLA C*04:01, HLA B*18:01, and HLA-DRB1*01 [6], and a family aggregation has been proposed.

In *in vitro* models, some cytokines have been implicated in the physiopathology of SAT, TNF-a, and miR-315 levels are upregulated, and both induce apoptosis and concur with the activation of the JAK2/STAT3 pathway and upregulation of miR-155-5p and (Interleukin) IL-6 expressions [7]. The COVID-19 pandemic proposed other pathways of thyroidal damage, the antigenic MHC (major histocompatibility complex) I-viral peptide is presented to $CD8^+$ (cytotoxic T lymphocytes) CTLs which activated CTLs trigger death signals to follicular thyroid cells by binding of their FasL and activating Fas signals, this union promotes the rupture of the thyroid follicle with the release of thyroidal hormones [8], and the release of thyroglobulin (TG), triiodothyronine (T3), and thyroxine (T4) causes thyrotoxicosis; finally, TSH is suppressed by a negative feedback loop of elevated thyroid hormones.

Other findings may involve the presence of low titers of autoantibodies and probably have only a secondary role after initial tissue alteration. T-lymphocytes sensitized against thyroid antigens may be found, and tissue samples contain large numbers of antigen-reactive T cells. However, these alterations are probably part of the inflammatory process after thyroid destruction.

In recent years, during the COVID-19 pandemic, the SARS-CoV-2 infection emerged as SAT triggering factor; this virus requires a receptor to enter the cell, which is an angiotensin-converting enzyme 2 (ACE2), and thyroid cells are rich in these enzymes [9].

Clinical Manifestations

Even if it is a self-limiting disease, some patients could require treatment in the initial phase of SAT. The natural history involves three phases that last over 3 weeks to 6 months [10]. The clinic begins with a prodrome of generalized myalgias, pharyngitis, low-grade fever, and fatigue; sometimes, it coincides with the presentation of any upper respiratory tract infection in the last 30 days [2]. After that, patients develop pain in the anterior region of the neck radiating to the ears, jaw, throat, or down to the sternum; other disorders that may arise from the same area should be distinguished. In SAT, the thyroid gland is affected asymmetrically and, on palpation, is extremely tender and may be accompanied by dysphagia. However, the number of painless SAT [5] has increased in recent years during the pandemic. In some cases, the thyroid gland can be enlarged, or thyroid nodules can be found on examination.

In the first phase, 50% of patients have thyrotoxicosis, with palpitation and nervousness lasting about 6 weeks. Even though the elevation of thyroid hormones and the clinical picture is mild, thyroid storm caused by SAT has been described. Loss of body weight and hematuria could be present and remits when the thyrotoxicosis remits [9]. With the depletion of thyroid hormone storage, there is a distinctive second phase of the disease consisting of hypothyroidism, usually lasting 6–12 months. In the last phase, the thyroid architecture and function are restored, and most patients return to euthyroidism without sequels of the disease, although 30% develop permanent hypothyroidism.

Biochemical Features

The first change at the initial stage of the disease is an increase in TG concentration. The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, and white blood cell (WBC) increase with about half of the patients presenting neutrophilia and a positive correlation with granulocyte colony-stimulating factor (G-CSF). Hematological alterations typical of SAT are higher platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio [11]. During the thyrotoxic phase, there is an increment in thyroid hormones, with a T4:T3 ratio greater than 20, that reflects the proportion of stored hormones and helps to differentiate from the actual hyperthyroid states (e.g., Graves' disease, where the gland is hyper-functional). Initially, when hypothyroidism develops, the thyroid-stimulating hormone (TSH) levels remain suppressed, and peak levels of laboratory abnormalities are reached within 1 week after disease onset. If the first studies are taken by this time, it could be misdiagnosed as a central hypothyroidism. Later, there is a compensatory response with high TSH, T3, and T4 within the normal limits.

Few patients show a positive thyroid antibody pattern; the 15.5% antithyroid peroxidase antibodies (TPOAb) and 33.3% antithyroglobulin antibodies (TgAb) could be the consequence of antigen release by thyroid follicle damage; this transient antibody positivity is significantly lower than those observed in Hashimoto Thyroiditis [12], and they do not correlate with the thyroid function.

Diagnostic Criteria

Despite the advances in diagnostic methods, the diagnosis often needs to be completed in SAT. The levels of thyroid hormone vary with time; during the first stages, there is a temporary increase of free T4, but later, the levels decline, even though hypothyroidism usually develops later in the course of the disease. The radioactive iodine uptake at 24 h is less than 5%. The initial thyroidal ultrasound screening for thyroid nodules had a sensitivity of 72.4%, specificity of 89%, positive

Table 48.1 Main characteristics of subacute thyroiditis

Diagnostic test	Expected result in SAT
TSH levels	Suppressed at initial stages, posterior back to normal
RAIU at 24 h	Positive in less than 5%
Anti-TPO antibodies	Absent, could be positive in Hashimoto thyroiditis or Graves' disease
CRP and ESR	High
Thyroidal ultrasonography	Flake hypoechoic area, nodular changes. Doppler shows low resistance and low speed of arterial blood flow
Thyroidal biopsy	Granulomatous infiltrate and giant cells
T4 and T3 levels	Initially high, posterior depletion

Anti-TPO antithyroid peroxidase, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *RAIU* radioactive iodine uptake test, *T3* triiodothyronine, *T4* thyroxine, *TSH* Thyroid-stimulating hormone

Table 48.2 Diagnostic criteria of subacute thyroiditis (SAT) [9]

Main criteria (all should be met)	Additional criteria (at least one should be met)
1. Laboratory: elevation of ESR or CRP	1. Hard thyroid swelling
2. Ultrasound: hypoechoic area/areas with blurred margin and decreased vascularization in US	2. Pain and tenderness of the thyroid gland/lobe
	3. Elevation of serum FT 4 and suppression of TSH
	4. Decrease radioiodine uptake
	5. FNAB result typical for SAT

ESR erythrocyte sedimentation rate, *CPR* C-reactive protein, *T4* thyroxine, *TSH* thyroid-stimulating hormone, *FNAB* Fine needle aspiration biopsy, *SAT* Subacute thyroiditis

predictive value of 80.4%, and negative predictive value of 83% in SAT patients [13]. The Doppler ultrasonography shows a heterogeneous parenchyma with flow reduction in the hypoechoic areas and a normal or only slightly increased flow in the rest of the gland [14]. It has been reported that changes in the thyroid gland size are smaller than in healthy subjects. Despite improvement in clinical and serological manifestation, the size of the gland remains smaller [15]. The results obtained in diagnostic tests in SAT are summarized in Table 48.1.

New classification criteria have been proposed (see Table 48.2), considering the novelty characteristics found after the COVID-19 pandemic [9].

These criteria recommend that in case of doubt and in patients that show no improvement on short-term follow-up, fine needle aspiration biopsy (FNAB) should be performed to exclude malignancy. COVID-19 must also be considered as a triggering factor so in patients with/after SARS-CoV-2 infection who present a new onset or worsening tachycardia or arrhythmias, deterioration of fatigue or malaise or present laboratory markers of thyrotoxicosis even in patients with the painless thyroid gland [9].

Prognosis

Recurrent SAT pain is related to the presence of HLA risk haplotypes and occurs around 1–2% in patients [16], although some authors have reported a recurrence even in 20%. Hypothyroidism usually persists for 6 months or less and can continue for a year. Permanent hyperthyroidism state has been reported in 10–15% of cases and requires treatment forever. There are no prediction scores for the development of permanent hypothyroidism, but it has been studied a relation between this state and a higher peak of TSH, the delay in the treatment, the presence of anti-TPO antibodies and ibuprofen therapy [17]. Moreover, the lowest peak of TSH and shorter duration of thyrotoxicosis phases have been associated with the recurrence of SAT. Early elevated TSH value is related to incident hypothyroidism, and TSH values above 7.83 mIU/L and CPRO levels above 97.8 mg/L could be used as an indicator of hypothyroidism risk [15, 18].

Treatment

The aim of the treatment of SAT is to diminish pain and symptom control. The American Thyroid Association (ATA) recommends that patients with mild symptomatic SAT should be treated with non-steroidal anti-inflammatory drugs (NSAIDs) such as salicylic acid (600 mg orally every 6 h) or ibuprofen (400–800 mg orally every 8 h) and β-adrenergic-blocking drugs in case of thyrotoxic symptoms [1]. The mean time from the start of therapy to complete pain relief is 5 weeks. Some trials demonstrated that NSAIDs as monotherapy fail in half of the patients, so corticoids should be started in case of a lack of responses to NSAIDs or in patients with severe symptoms. The starting dose of corticoids is controversial; the ATA guidelines accept prednisone 40 mg daily for 1–2 weeks and gradual tapering over 2–4 weeks or prednisone 15 mg daily with tapering of 5 mg every 2 weeks [1]. The combination of corticoids with NSAIDs for 15 days had a lower frequency of side effects compared to long-term therapy with greater doses of corticoids for moderate to severe SAT. The symptoms may recur after withdrawal of treatment, but in these cases, the response is obtained with the reinstitution of treatment [16]. Patients with corticoids rather than NSAIDs are less likely to have permanent hypothyroidism [15].

Intrathyroidal steroid injection has been proposed, and it could provide a faster and safer approach in selected patients [19]. Otherwise, colchicine [20] has been described in patients with steroid-refractory recurrent SAT and even thyroidectomy in patients with persistent pain.

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49

Graves' Disease

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Abstract

Graves' disease (GD) is an autoimmune disorder mainly involving the thyroid gland. GD is the most common cause of hyperthyroidism. Autoantibodies provoke GD to the thyroid-stimulating hormone receptor (TSHR), prompting considerable thyroid hormone secretion. In addition, TSHR autoantibodies cause Graves' ophthalmopathy and pretibial myxedema. Even though the etiology of GD is unsure, some reports suggest a strong genetic factor in conjunction with unpredictable environmental determinants in an immunologically prone subject. Treatment options include antithyroid drugs, radioiodine, or surgery. However, new therapies are currently being evaluated. A multidisciplinary approach is needed to manage all aspects of GD, mainly thyroid eye disease, for which new therapeutic options are now available.

Introduction

Graves' disease (GD), also recognized as von Basedow disease, was established in the nineteenth century as a syndrome including an augmented and overactive thyroid gland, tachycardia, and ocular abnormalities. Relevant to our present conception of this condition was the finding of its autoimmune condition, which is a consequence of intricate interplays between genetic and environmental determinants [1]. GD may adversely impact health-related quality of life due to somatic and psychiatric manifestations and disability to work. In addition, GD has been related to a higher mortality risk [2]. Graves' hyperthyroidism (GH) was primarily assumed to be a consequence of considerable thyroid-stimulating hormone (TSH) secretion by the hypophysis. However, the finding of thyroid-stimulating hormone receptor antibody (TSHR-Ab) more than six decades ago established GD as an autoimmune disorder.

Autoantibodies, primarily TSHR-Ab, drive the disease, but underlying mechanisms are still not completely understood. These autoantibodies function as TSHR agonists and prompt thyroid cells to secret an abundance of thyroid hormones (TH). Increased levels of TH lead to several clinical features of GD. The approach to investigation and treatment of GD varies widely.

Epidemiology

GD is the most frequent cause of hyperthyroidism worldwide [3]; it affects around 2% of women and 0.2% of men. The female-to-male ratio is about 10:1. According to Nurses' Study II (NHSII) data, the 12-year incidence among females aged 25–42 was approximately 4.6/1000.

Population-based studies reveal that the incidence of GD is 20–40/100,000 inhabitants. GD is most prevalent in individuals between 20 and 50 years, and the greater part of subjects with hyperthyroidism aged <40 years are possibly expected to have GD [4]. A longitudinal study showed that the prevalence and incidence of GD were similar regarding iodine deficiency.

In general, the incidence of hyperthyroidism accords with population iodine nutrition, with higher rates of hyperthyroidism occurring in iodine-deficient regions, mainly owing to an excess of nodular thyroid disease in elderly patients. After 20 years, the incidence rate decreased with iodine supplementation [5]. This corroborates that, different

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from multinodular goiter, the prevalence and incidence of GD cannot be exclusively defined by iodine concentrations. Alternatively, due to concordance proportions and family features, genetic determinants of autoimmunity should be regarded in the presence of GD [1].

Graves ophthalmopathy (GO) has been estimated at 10 per 10,000 people and 16 per 10,000 people in Europe and Japan, respectively. Consequently, nearly 5% of individuals with GD have typical features of GO. Additionally, around 2% of them will develop severe ophthalmopathy with optic neuropathy, with 50% possibly requiring decompression surgery [6]. The frequency of pretibial myxedema (PTM) with GO is around 0.15 per 10,000 people, an uncommon complication of GD.

Risk Factors

The occurrence of GD requires both environmental and genetic determinants involving epigenetic mechanisms and the microbiota, leading to an immunopathogenetic mechanism. GD is more prevalent in five in females than men. In women, the occurrence of GD remains stable after menopause. The previous data is possibly explained by the X chromosome involvement rather than sex hormones [7].

The incidence of GD fluctuates in and around pregnancy. The peak incidence of GD has been reported in early pregnancy and 12 months after delivery. On the other hand, a high prevalence of infertility has been observed among women with GD, and the risk of this disorder during pregnancy is low [8]. GD tends to improve in women in advanced pregnancy because of the role of regulatory T cells. In contrast, after delivery, the risk of postpartum autoimmune thyroid disease increases.

For years, some infectious agents, such as *Yersinia enterocolitica*, *Helicobacter pylori* (*H. pylori*), and viral infections (e.g., hepatitis C), have been described as potential contributors to the pathogenesis of GD. Furthermore, another analysis reported that interferon-α (IFNα) led to the lysosomal degradation of thyroglobulin, releasing pathogenic peptides that might prompt thyroid antigens to the immune system.

Immunopathogenesis of Graves' Disease

GD is an autoimmune thyroid disorder primarily driven by stimulating TH receptor antibodies (TSHR-Ab) or immunoglobulins (TSI). These antibodies specifically target the thyrotropin receptor (TSHR), leading to uncontrolled uptake and iodination of iodine, the release of TH, and the manifestation of clinical thyrotoxicosis. Approximately 79% of GD risk is inherited, while 21% is environmental. In addition, 70% of autoimmune thyroid disease (AIDT) genes affect T-cell function. GD factors include estrogens, X-inactivation, and microchimerism. Smoking, extra iodine, selenium, vitamin D, and agent orange exposure increase GD risk. Chronic HCV hepatitis and thyroid autoimmunity/hypothyroidism have been associated with mixed cryoglobulinemia and GD risk [9]. Systemic autoimmune diseases, like Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis, among others, may have thyroid autoantibodies and thyroid dysfunction. Psoriatic arthritis and dermatological problems are also linked to GD [10].

GD pathogenesis involves CXCR3 and its chemokines CXCL9, CXCL10, and CXCL11. Th1 chemokines from injured cells attract Th1 lymphocytes. Inflamed tissues attract Th1 cells, which produce IFN-gamma and TNF-alpha and boost Th1 chemokines, creating an amplification feedback loop. Later, in the quiescent phase of GD, the immune response switches from Th1 to Th2 [11].

GD involves circulating thyroid-stimulating antibodies (TSAb), producing extrathyroidal manifestations (GO, pretibial myxedema]. Th1 chemokines and their CXCR3 receptor dominate the immune pathogenesis of GD and GO during the active phase. Antigen-specific treatment can induce T-cell tolerance in GD by immunizing with TSH-R peptides. Rituximab, cytokine-targeting medicines, and teprotumumab (a human monoclonal anti-IGF-1R-blocking antibody) worked in GO [12]. Furthermore, in treating patients who have GO, one clinically effective tool is the measurement of TSHR-Ab, particularly stimulating antibodies.

Th17 and Th22 cells also are related to GD. A case-control study discovered higher pathogenic Th17 and Th22 lymphocyte concentrations in peripheral blood from autoimmune thyroid disease patients. GD thyroid glands also had these cells. These cells also correlated with illness activity, duration, and ophthalmopathy.

Plasmacytoid dendritic cells (PDC) increase in GD patients' perithyroidal lymph nodes but not in multinodular goiter patients. Thus, PDC migration and storage at anatomical connecting points between the thyroid gland and orbita may be crucial for persistent autoimmune stimulation. PDC may play a novel function in GD and a therapeutic target.

Autoimmune thyroid disorders are linked to *H. pylori* and HCV. Still unknown are pathophysiologic processes. Molecular mimicry is *H. pylori's* central mechanism. Hepatitis C virus may cause thyroid autoimmunity by exacerbating the production of thyroid autoantibodies. Still, some believe that IFN-alpha treatment upregulates MHC class I and induces CD40+ cell ligation to thyrocytes. Thyroid autoimmune illnesses have been linked to microbes such as *Toxoplasma gondii*, HIV, Herpes, and others. How these last microbes cause thyroid autoimmunity is unknown. It's yet unproven. More research is needed to understand how these bacteria interact and how to treat these patients [13].

When excessive TH is present, mast cells overexpress co-stimulating CD86, and the thyroid gland becomes inflamed. This suggests they may present auto-antigens. Interferon-gamma levels rise significantly, indicating cytokine effect on pathology [14].

Infection with SARS-CoV-2 has been related to the development of destructive thyroiditis and has been shown to promote thyroid autoimmunity. In addition, the SARS-CoV-2 BNT162b2 mRNA vaccine can alter autoimmunity in the thyroid [15].

Clinical Manifestations

Hyperthyroidism

The clinical presentation, severity, and duration of hyperthyroidism fluctuate considerably, depending on the patient's age. The most prevalent symptoms are weight loss, fatigue, heat intolerance, tremor, and palpitations. In elderly persons, weight loss, hyporexia, and cardiovascular manifestations, such as atrial fibrillation, are more frequent than in younger. In younger than 60 years, palpable goiter is a common feature [16]. In patients aged <50 years, neurogenic manifestations (e.g., tremors and anxiety) prevail. Generally, it is common for GD to have a sudden onset of symptoms. Extrathyroidal manifestations, like GO, are often related to more severe hyperthyroidism and a larger goiter.

Extrathyroidal Manifestations

Ophthalmopathy

Orbital affection is a corresponding result of the primary autoimmunity within the thyroid. GO may disfigure and can threaten sight. Disease progression, which may last up to 3 years, is witnessed. Some relevant ocular manifestations in the active phase include proptosis, eyelid swelling, diplopia, dry eye, excessive tearing, and visual discomfort. In contrast, the ocular symptoms and signs turn stable in the inactive phase. In a cohort of patients with GD, the occurrence of diverse manifestations: eyelid retraction (due to increased sympathetic tone) (92%), exophthalmos (62%), extraocular muscle dysfunction (43%), ocular pain (30%), increased lacrimation (23%), and optic neuropathy (6%). At the subsequent stage, extraocular muscles become fibrotic, leading to limited motility.

GD-Associated Dermatopathy

In patients with GD and mainly with severe GO, the prevalence of thyroid dermatopathy is 1–4%. Skin lesions are commonly localized on the pretibial region, although they can occur else but can occur elsewhere (elbows, feet, and toes). PTM is frequently presented as an erythematous, non-pitting thickening of the skin in the pretibial region. In severe cases, skin lesions show larger fleshy nodules and elephantiasis myxedema in most serious occurrences. The biopsy findings include dermal deposition of glycosaminoglycans. Although not malignant, PTM is usually complex to treat. The reason for explaining the presentation of PTM in the lower legs is unknown, but deficient circulation and repeated injuries are possible determinants. Currently, the pathophysiology of PTM is unclear, but molecular pathways resembling those implicated in GO are nearly definitely involved in TSHR display in dermal fibroblasts.

Thyroid Acropachy

Acropachy, similar to clubbing of the fingers or toes, occurs mainly in those patients with dermatopathy and GO. Thyroid acropachy has characteristic radiologic findings, such as periosteal new bone formation. An augmented cardiac output in patients with severe hyperthyroidism is the leading hypothesis for acropachy by inducing peripheral bone changes. Acropachy is currently an uncommon manifestation due to early GO detection and management (Table 49.1).

Table 49.1 Major symptoms and physical signs of Graves' disease

Frequent symptoms
Palpitations, dyspnea, tremor, fatigue, muscle weakness, heat intolerance, increased sweating, increased stool frequency, anxiety, insomnia, pruritus, thirst and polyuria, menstrual disturbances (oligomenorrhea or amenorrhea), loss of libido, eye symptoms (swelling, pain, redness, double vision)
Physical signs
Tachycardia, atrial fibrillation, systolic hypertension, increased pulse pressure cardiac failure, weight loss, fine tremor, hyperkinesis, hyperreflexia, moist skin, palmar erythema and onycholysis, muscle weakness, hair loss, diffuse, palpable goiter and thyroid bruit, mood changes (e.g., mania or depression)
Extrathyroidal physical signs
Ophthalmopathy, eyelid lag, retraction, or both, exophthalmos, double vision, (extraocular-muscle dysfunction), periorbital edema, chemosis, scleral injection, exposure keratitis, optic neuropathy, localized dermopathy, acropachy

Diagnosis and Screening

Although GD is the most frequent cause of hyperthyroidism, the evaluation of differential diagnosis should be considered. Common causes of hyperthyroidism are toxic multinodular goiter, thyroid adenoma, destructive thyroiditis, factitious hyperthyroidism (e.g., struma ovarii), and amiodarone-induced hyperthyroidism (Table 49.2). An accurate etiological diagnosis is fundamentally relevant as treatment alternatives vary, especially regarding the origin of hyperthyroidism. An established diagnosis of GD can frequently be set rapidly on a clinical basis: symptoms in patients with any sign of GO and a diffuse goiter can help to confirm the diagnosis. When ultrasonography (US) is feasible, nodules can be ruled out. Nevertheless, in some circumstances, the diagnosis could be more promptly apparent on clinical grounds, for instance, in individuals who initiate only hyperthyroidism with no other distinctive manifestations. Thyroid overactivity is commonly diagnosed by assessing serum TSH concentrations and free thyroxine concentrations.

In some cases, serum TSHR autoantibodies detection helps establish a GD diagnosis. When the autoantibodies test results are negative, a radioiodine uptake and thyroid scan should be made to confirm the diagnosis. In GD, the radioactive iodine uptake test (RAIU) is described by a normal or increased percentage uptake. In contrast, a low or absent uptake is characteristic of thyroiditis, except if an iodine-related source inhibits the uptake or direct impairment to the thyroid cells occurs.

TSHR Autoantibodies Tests

The diagnosis of GD is confirmed when serum TSHR autoantibodies accompany the hyperthyroidism. As first-line tests, complex and expensive bioassays utilizing TSHR-transfected cells are not selected when patients have already been diagnosed with hyperthyroidism. Alternatively, most laboratories' third-generation receptor binding tests for TSHR autoantibodies now exhibit outstanding analytical achievement. Current assays show high sensitivity and specificity (>95%) for diagnosing GD in patients with evident hyperthyroidism. In contrast, the capability of these assessments in individuals with subclinical hyperthyroidism has yet to be consistently demonstrated in cohort studies. In those cases, bioassays with slightly higher sensitivity than binding assays can be an option in cases where the receptor assay is negative. Additionally, a RAUI and thyroid scan might aid in certain patients. However, many patients in this group are affected by thyroiditis.

Thyroid Imaging

The evaluation of thyroid disorders sometimes requires the use of radiology testing. Thyroid US was broadly utilized to distinguish solid nodules from cystic ones. With the emergence of top-notch and inexpensive portable US equipment, nodules are instantly ruled out in every patient with GD. The obstacle to this strategy can be overdiagnosing of thyroid cancers. Beyond this limitation, the US has become a relevant and pragmatic tool.

Although computed tomography (CT) and magnetic resonance imaging (MRI) scans can detect thyroid nodules, they are less accurate and do not aggregate more insight into the ultrasonographical evaluation except when searching for enlarged lymph nodes in thyroid cancer.

CT and MRI of the orbit are justified when the reasons for ocular symptoms are unclear. These imaging assessments are helpful in the differentiation of extraocular muscle enlargement from fat distention, particularly in subjects with asymmetric proptosis, excluding orbital tumors and arteriovenous malformation. Evaluating the activity and severity of ophthalmopathy, which can commonly be accomplished by clinical examination, aids in guiding the management.

Table 49.2 Cause of hyperthyroidism according to diagnosis tests

Condition	TSH autoantibodies	Thyroglobulin levels	Radioiodine uptake and thyroid scan pattern	Thyroid ultrasonography and Doppler
Graves' disease	+	↑	Normal or high; diffuse uptake	Normal or hyperechoic signals; high or normal flow
Toxic multinodular goiter	_	↑	Normal or high; patchy uptake	Multiple nodules; high or normal flow
Destructive thyrotoxicosis	_	↑	None or very low uptake	Hypoechoic signals; low flow
Toxic adenoma	_	↑	Normal or high; unifocal uptake	Single nodule; high or normal flow
Factitious thyrotoxicosis	_	Undetectable	No uptake	Normal signals
Struma ovarii	_	↑	No uptake	Normal signals
Amiodarone induced, type I	_	↑	Minimal or no uptake	Variable signals
Amiodarone induced, type II	_		No uptake	Normal signals; low flow

TSHR thyroid-stimulating hormone receptor

Various other imaging approaches, such as orbital US, scintigraphy with radiolabeled octreotide, gallium scanning, and thermal imaging, might help define the orbital disease [17].

RAIU is a measurement of thyroid function but does not involve imaging. In low TSH levels, high or normal values of RAIU denote TSH-independent activation of TH synthesis and release, showing GD. Low values of RAIU (<1%) can imply destructive thyrotoxicosis or factitious thyrotoxicosis (e.g., extrathyroidal source of TH or struma ovarii, in which TSH is inhibited, consequently suppressing RAIU). A diffuse pattern of RAIU establishes the diagnosis of GD. Contrarily, a patchy pattern shows multinodular or uninodular toxic goiter. In the past, RAIU was considered a gold standard for diagnosis; however, because it is expensive, recent developments in TSHR binding assays, and the extensive accessibility of US, it has ceased to apply.

Diagnosing GD might be more difficult in pregnant women when TSHR autoantibody tests are negative. Some relatively common manifestations in pregnancy, such as palpitations and perspiration, in conjunction with high serum TH concentrations related to increased estrogen production, could lead to misinterpretation. In addition, some patients have low TSH in the early phase of pregnancy due to the effect of human chorionic gonadotropin on the thyroid. As pregnancy advances, augmented immune tolerance often leads to the disorder becoming inactive and seldom requires management. In some females with persistent manifestations, elevated concentrations of TSHR autoantibodies help indicate a diagnosis.

The harmful impact of active thyroid disorder on pregnancy has earned limited concern despite adverse outcomes of this condition, such as pre-eclampsia, stillbirth, and preterm delivery. Recently, a systematic review showed a frequency of 0.64% of evident hyperthyroidism during pregnancy [18]. More and more, many females are screened for TH during pregnancy worldwide.

Treatment Options Graves' Disease

Thioamide antithyroid drugs (ATDs) and radioactive iodine (RAI) have been utilized for more than 60 years for GD treatment. These are the three established treatment modalities for GD and total thyroidectomy. Since the 1950s, systemic glucocorticoids have been widely used in active GO. Immunosuppressive therapies, such as rituximab, azathioprine, tocilizumab, and cyclosporin, have been investigated to treat GD; however, their adverse effects limit their application [19].

Nonetheless, the risk of toxicities with the administration of ATDs is low; however, there are severe or potentially life-threatening toxicities, such as agranulocytosis, hepatotoxicity, pancreatitis, and antineutrophil cytoplasmic antibodies (ANCA) positive vasculitis. In addition, those therapeutic agents are related to a high relapse rate after treatment cessation. Effectively, thyroid ablation by RAI or total thyroidectomy requires lasting TH replacement [20].

Various new treatments have been made to treat GH in the past few years. They do this in several ways, including (1) removing B cells, (2) stopping B/T-cell interactions through the CD40-CD154 costimulatory pathway, (3) restoring immune tolerance to TSH-R, and (4) blocking TSH-R.

ATX-GD-59

Two immunodominant epitopes (antigen-processing independent epitopes) originating from the human TSH-R sequence (ATX-GD-59) were enough to inhibit the T-cell and TSH-R-Ab responses. In clinical studies, ATX-GD-59 showed that around 70% of the patients had a full or partial response, and most people well tolerated it. Most (85%) treatment-related side effects were mild reactions at the injection site.

Iscalimab

Iscalimab is a pathway-blocking, Fc-silenced (nondepleting), completely human, anti-CD40 monoclonal antibody. It suppresses the activation of leukocytes induced by CD154 in vitro. A recent phase 2 study, a proof-of-concept experiment, assessed iscalimab's safety and efficacy in GH. Forty-seven percent of the patients reached biochemical euthyroidism by week 24. Iscalimab significantly reduced TSH-R-Ab levels and no major safety concerns; iscalimab was well tolerated.

TSH-R Small-Molecule Ligands

In vitro, TSH-R activation can be stopped by a few small-molecule drugs. As a TSH-R blocker, NIDDK/CEB-52 stopped both TSH and TSH-R-Ab from GD patients from turning on TSH-R.

TSH-R-Blocking Antibody

K1-70, a human TSH-R-blocking monoclonal antibody, was discovered in a patient with high TSH-R-Ab levels who developed hypothyroidism. It dose-dependently lowered fT4 levels and inhibited M22's stimulating effect in rats. A phase 1 open-label trial currently assesses the safety, tolerability, pharmacokinetics, and pharmacodynamics of K1-70 doses in GD patients (ClinicalTrials.gov: NCT02904330).

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Postpartum Thyroiditis

50

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and Mario García Carrasco

Abstract

Postpartum thyroiditis (PT) is the most frequent thyroid dysfunction, excluding Graves' disease (GD), during the first postpartum year in euthyroid women, with a prevalence of 5–10%, depending on the sociodemographic conditions. The most important risk factor for this disease is type 1 diabetes and its association with immunological illnesses such as Sjögren's syndrome, systemic lupus erythematosus, chronic viral hepatitis, systemic sclerosis, previous thyroid disease as well as thyroid peroxidase antibodies (TPOAb) or antithyroglobulin antibodies (TgAb) presence. If there is clinical suspicion of PT, TPOAb should be performed because of its adequate sensitivity profile for this disease. In classic PT, 20% of women will develop a phase of thyrotoxicosis, followed by hypothyroidism that recovers to an euthyroid state in 50% of cases. Around 20% of patients will have permanent hypothyroidism 12 months after the onset.

PT is treated with Levothyroxine. Making a prompt diagnosis will avoid using other interventions that affect the patient and her son during the critical stage of lactation.

Keywords

Postpartum · Thyroiditis · Pregnancy · Hypothyroidism · Hyperthyroidism

Introduction

Postpartum thyroiditis (PT) is a thyroid dysfunction, excluding GD, that occurs between the second and twelfth months after delivery. It can also occur after a spontaneous abortion or induced abortion in women with or without a preexisting thyroid autoimmune disorder. PT occurs in 33–50% of women with positive TPOAb. Typically, they can develop in two phases, the first with thyroid hyperfunction and the second with a hypothyroidism state. It generally disappears spontaneously a year after delivery, although thyroid hypofunction may persist [1–3].

Epidemiology

In the postpartum period, approximately 5–10% of women can experience PT within 12 months after delivery. However, PT can also occur after miscarriage or pregnancy loss, as well as in women on levothyroxine replacement for underlying *Hashimoto thyroiditis* (HT). The incidence of PT varies depending on factors that women have. For example, the disease will occur in 33–50% of women with positive TPOAb, 25% with type 1 mellitus, 50–70% in women with prior thyroid dysfunction (such as GD) and 70% of women who have presented PT in a previous pregnancy will give flares in subsequent pregnancies [1–5].

Pathogenesis

Genetic modifications can modify the development of PT. A genetic study carried out in patients with two different types of thyroid autoimmune disease, Hashimoto's thyroiditis (HT) and PT, demonstrated the presence of the GG genotype in the cytotoxic T lymphocyte CT60 of the CTLA-4 gene, which increases the production of TPOAb and TgAb. The level of TPOAb was significantly higher in the GG genotype

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(423 U/mL) compared to AA (12 U/mL) and AG (130 U/mL), $p < 0.006$ [6].

During pregnancy, human chorionic gonadotropin (hCG) production increases thyroid hormone production and decreases thyroid-stimulating hormone (TSH). Estrogens (E) and progesterone (P4) change the helper T cells (Th) balance, increasing the activity in cells type 2 (Th2) and decreasing the activity of type 1 and type 17 (Th1/Th17). Th2 cells release anti-inflammatory cytokines, such as interleukin 4 (IL-4), interleukin 5 (IL-5), and interleukin 10 (IL-10). A decline in action of Th1 is accompanied by a reduction of pro-inflammatory cytokine production: interleukin 2 (IL-2), interferon-gamma (IFN-γ), and tumor necrosis factor-alfa (TNF-α). Th1 and Th2 are stable during pregnancy due to $CD4^+$ $CD25^+$ regulatory T cells (T cells regs) activity. The expansion of T cells regs during gestation is owing to the production of fetal antigens and the estrogen-stimulated expression of several chemokines. In the puerperium, the number of T cells declines rapidly, allowing Th1 cells to become the dominant subset, releasing pro-inflammatory cytokines and exacerbating autoimmune diseases [1–3, 6–8].

The prevalence of TPOAb and TgAb in pregnant women has been calculated from 5% to 14% and 3% to 18%, respectively. It seems that thyroid autoimmunity has an additive or synergistic effect, increasing the risk of spontaneous abortion and prematurity when subclinical maternal hypothyroidism is presented [2]. These antibodies are associated with a higher chance of spontaneous abortion, preterm birth, progression to hypothyroidism, and development of postpartum thyroiditis than even in women without thyroid pathology before pregnancy. TPOAb triggers postpartum thyroiditis and hypothyroidism (33–50%) by promoting increased IL-2 production and natural killer (NK) cell activation. Current studies have shown that thyroid-specific peroxidase can also be found in the endometrium and placenta, which may explain the presence of spontaneous abortion in positive TPOAb patients. Although TPOAb and TgAb cross the placenta, these antibodies do not cause thyroid disorders in fetuses. Therefore, pregnant women with positive TPOAb antibodies must be strictly monitored using TSH levels throughout the pregnancy, even at 3 and 6 months postpartum [1–3, 6–8].

Pathologic Features

PT shows a diffuse, non-specific inflammatory infiltrate in the biopsy; it is rarely required histopathologic material to support the diagnosis. When a biopsy is performed, it can be identified as a common focal or diffuse chronic thyroiditis with variable infiltration of lymphocytes and sometimes shows mild hyperplasic changes of follicles. The immunohistochemical staining shows T lymphocytes more than B ones [5, 9, 10].

Approach and Biomarkers

Approximately one-third of women with PT present the classic phases of (thyrotoxicosis-hypothyroidism-recovery), while the rest present incomplete forms [2]. The quantification of TSH, T3, and T4 is essential; TSH levels can be suppressed with variable elevation of T4 and T3 in the initial phase of hyperthyroidism, and later comes the highest level of TSH, with varying levels of T3 and T4. Finding positive TPOAb and TgAb supports the presence of autoimmune thyroiditis (Table 50.1) [3–5, 11]. TPOAb and microsomal disease antibodies (MCAb) represent lymphocyte infiltration into the thyroid. Therefore, they are useful markers to predict “subclinical autoimmune thyroiditis” after delivery [1–3, 6–8]. However, current studies have reported that TPOAbs are not specific and can frequently occur without thyroid dysfunction or other autoimmune diseases [12].

During pregnancy, there are five alterations in thyroid function: (1) the transient increase in human chorionic gonadotropin during the first trimester, which stimulates the TSH receptor; (2) the increase in thyroxine-binding globulin induced by estrogens during the first trimester, which is maintained throughout the pregnancy; (3) alterations in the immune system that dysregulate thyroid function; (4) the increase in the metabolism of thyroid hormone by the placenta; and (5) increased urinary iodine excretion, which can cause a marginal iodine deficiency [8].

Antithyroid antibodies are associated with an increased risk of unexplained infertility, miscarriage, recurrent miscarriage, preterm birth, and PT [2, 13]. Pregnant women with type 1 diabetes should have TSH and TPOAb determinations; in case of positive antibodies, controls should be performed every 3–6 months [13–15].

There is an increased risk of PT in pregnant women with underlying thyroid dysfunction and gestational diabetes. All pregnant women with gestational diabetes, or women who have had prior thyroid dysfunction, should be screened for

Table 50.1 Functional thyroid tests

Hormone	Normal values
TSH (mIU/L)	
First trimester	0.03–4.24
Second trimester	0.13–4.84
Third trimester	0.30–5.57
TSH for Normal Thyroid function	0.3–4.2
Free T4 (ng/dL)	
First trimester	0.84–1.43
Second trimester	0.68–1.21
Third trimester	0.67–1.12
T3 (ng/dL)	2.4–6.3
TPOAb (UI/mL)	<16

TSH thyroid-stimulating hormone, *T3* triiodothyronine, *T4* thyroxine, *TPOAb* autoantibodies thyroid peroxidase [3, 11] thyroid hormone abnormalities during pregnancy and for 1 year after [5, 8, 13–16].

A systematic review including 63 studies reported the prevalence of overt thyroid dysfunction in pregnant women [14].

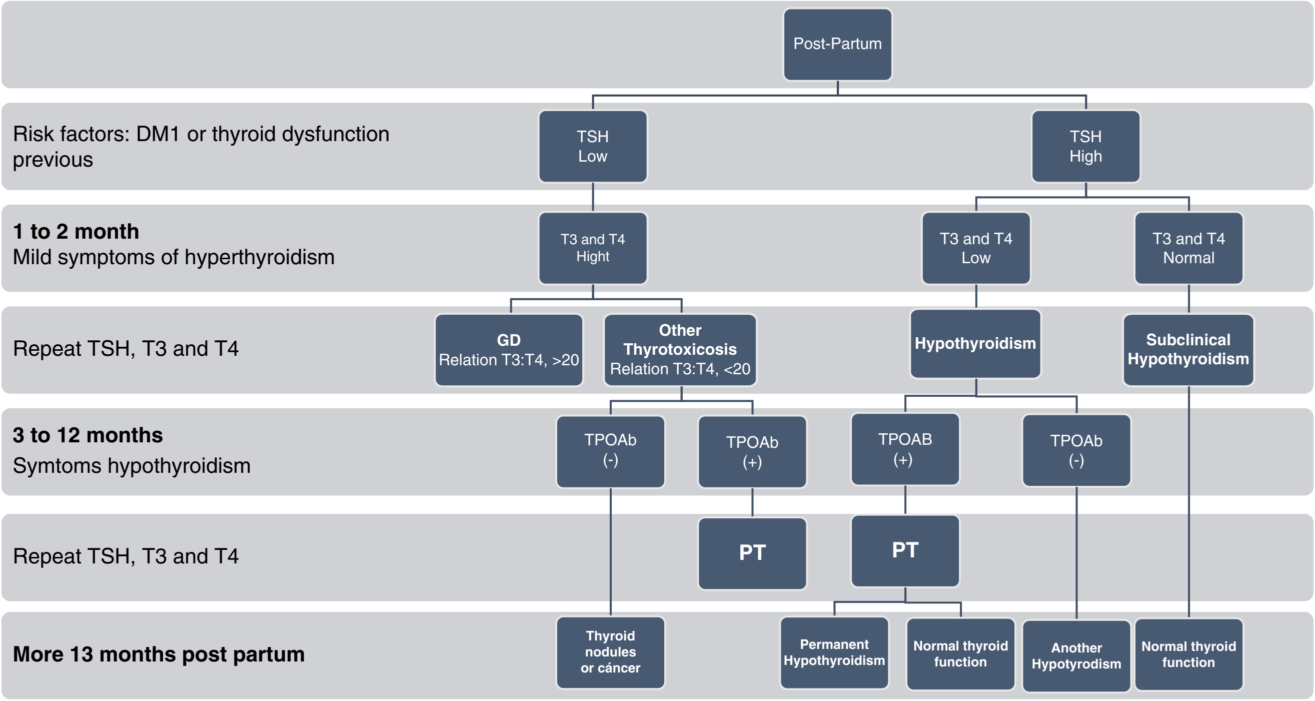
Clinical Manifestations

During the symptomatic phase, women with positive TPOAb develop fatigue (78%), irritability (61.9%), lack of concentration (57.9%), memory disturbances (57.4%), pain (52.3%), dry skin (51.3%), heat intolerance (41.6%), palpitations (10.2%) and depression symptoms (33.5%) [17]. Usually, the onset of PT begins between the second and third month after delivery [18]. One-third of women with PT classic show thyrotoxicosis and hypothyroidism, while incomplete forms occur in the remainder. The thyrotoxicosis period can occur 4–8 weeks after delivery and last from 1 to 2 months (20–40% of cases). The hypothyroidism phase can persist and last another 4–6 months (40–50%) until the thyroid gland recovers [2, 3, 5, 12]. In 20% of women with PT, hypothyroidism becomes permanent after 12 months [1]. PT can recur in 70% of subsequent pregnancies [4, 5].

Diagnostic Criteria

There are no specific criteria to diagnose PT because most women may be asymptomatic or develop low symptoms of hyperthyroidism (irritability, heat intolerance, fatigue, palpitations and weight loss). However, in post-partum women with pre-existing thyroid disease, type 1 diabetes, or TPOAb positivity, PT should be suspected [1, 4]. It is important to discern the thyrotoxic phase of postpartum thyroiditis from GD. Antibodies against the thyrotropin receptor (TRAb) are specific and sensitive biomarkers for GD. Furthermore, the T3:T4 ratio is usually higher (>20:1) in GD due to the preferential production of T3 [2]. Radiocontrast scintigraphy should be considered in GD. In PT, absorption is nil, while in GD is too high. However, scintigraphy with radioactive iodine uptake is contraindicated during lactation [5, 13].

Postpartum women with low TSH levels and moderately free T4 and total T3 levels could be in a thyrotoxic phase of PT, and testing must be performed every 4–8 weeks after delivery. If TSH is elevated and free T4 is low or normal, there may be a hypothyroid phase of PT. Therefore, taking TPOAb levels and re-evaluating the patient to rule out another disease are suggested (Fig. 50.1) [3–5, 11].


Post-Partum
Risk factors: DM1 or thyroid dysfunction previous
TSH Low
TSH High
1 to 2 month
Mild symptoms of hyperthyroidism
T3 and T4 Hight
T3 and T4 Low
T3 and T4 Normal
Repeat TSH, T3 and T4
GD Relation T3:T4, >20
Other Thyrotoxicosis Relation T3:T4, <20
Hypothyroidism
Subclinical Hypothyroidism
3 to 12 months
Symtoms hypothyroidism
TPOAb (-)
TPOAb (+)
TPOAB (+)
TPOAb (-)
Repeat TSH, T3 and T4
PT
PT
More 13 months post partum
Thyroid nodules or cáncer
Permanent Hypothyroidism
Normal thyroid function
Another Hypotyrodism
Normal thyroid function

TSH: thyroid-stimulating hormone, T3: triiodothyronine, T4: thyroxine, TPOAb: autoantibodies thyroid peroxidase, GD: graves'disease, PT: postpartum thyroiditis [13].

Fig. 50.1 Diagnostic algorithm of postpartum thyroiditis. *TSH* thyroid-stimulating hormone, *T3* triiodothyronine, *T4* thyroxine, *TPOAb* autoantibodies thyroid peroxidase, *GD* Graves' disease, *PT* postpartum thyroiditis [13]

Treatment

Pregnant women with hypothyroidism should increase their dose of levothyroxine between 20% and 30% (two more tablets per week). A study showed the risk reduction of first-trimester hypothyroidism and TSH suppression through this strategy when compared to an increase of three tablets per week [11, 18].

International guidelines recommend that women with PT and severe symptoms of thyrotoxicosis receive beta-blockers (BB) for a few weeks and even up to a few months. These agents do not affect breastfeeding and can block the production of T4 and thyroglobulin, reducing heart palpitations, fatigue, anxiety, and sweating. Propranolol or metoprolol can be used, starting with low doses and increasing gradually. In the hypothyroidism phase, the symptoms will depend on TSH levels; generally, a few months after birth, they become stable. The American Thyroid Association (ATA) recommends starting treatment with levothyroxine when TSH levels are up to 10 mlU/L with positive TPOAb. In case of TSH > 10 mIU/L, negative TPO and the presence of symptoms, treatment with Levothyroxine should also be begun. Therefore, starting treatment with Levothyroxine will depend on the TSH levels and symptoms but not on the positivity of the TPOAb. However, this distinction must be made between patients because TPOAb presence is associated with an increased risk of permanent hypothyroidism [4, 5, 18]. This information is shown in Table 50.2.

The levothyroxine therapy effects were evaluated in a retrospective study that included 5405 pregnant women with subclinical hypothyroidism. The authors found that starting treatment at 28 weeks reduced the risk of miscarriage by 38% compared with untreated women (OR 0.62; 95% CI 0.48–0.82, $p < 0.01$), but treated women increased the possibility of preterm birth (OR 1.60; 95% CI 1.14–2.24, $p = 0.01$), gestational diabetes (OR 1.37; 95% CI 1.05–1.79, $p = 0.02$), and preeclampsia (OR 1.61; 95% IC 1.10–2.37, $p = 0.01$). The possibility of spontaneous abortion was lower in women who received treatment from a previous TSH level of 4.1–10 mIU/L but not if the TSH level was 2.5–4.0 mIU/L (OR 0.45; 95% CI 0.30–0.65 vs. OR 0.91; 95% CI 0.65–1.23, $p < 0.01$, respectively) [19]. A prospective study showed a reduction in the risk of preterm birth and neonatal hospitalization by 70–83% when thyroid treatment was started [20].

The symptoms of PT and postpartum depression can be similar; however, a study did not show an association between thyroid dysfunction and postpartum depression [21]. Even though thyroxine levels have been found in maternal breast milk (0.83 micrograms/L), thyroxine does not affect the thyroid function of neonates during lactation [7]. ATA recommends Levothyroxine treatment for subclinical hypothyroidism during pregnancy (Table 50.2) [4].

The use of antithyroid drugs during the thyrotoxicosis phase can be controversial. Methimazole/carbimazole can be transferred to breast milk in concentrations of approximately 0.1–0.2% and <0.1% for propylthiouracil. These concentrations are deficient and unlikely to mean a risk to the son. Therefore, ATA recommends that the lowest effective dose of methimazole (<20 mg/day) or propylthiouracil (<450 mg/day) can be used safely in lactating women [4, 13].

Radioactive iodine (RI) is contraindicated in breastfeeding women, that is why other radiopharmaceutical options must be sought. RI may be considered when hyperthyroidism persists after 1 year, and there is no response to treatment with antithyroid drugs [7, 13]. Iodine intake should continue in lactating women, 250 µg/day through diet and supplements [4, 13].

Prognosis

Most women with PT recover normal thyroid function 1 year after birth, and longitudinal studies (follow-up of 3–12 years approximately) reported permanent hypothyroidism around 20–50%. A history of PT with normal thyroid function increases up to 70% probability of PT in subsequent preg-

Table 50.2 Recommendations of the American Thyroid Association (ATA) for treatment of subclinical hypothyroidism in pregnancy

Therapy		TSH	TPOAb[a]	Recommendation and evidence quality
Levothyroxine	Not	TSH within the PSR or <4 mIU/L if unavailable	Negative	Strong recommendation, high-quality evidence
	Consider	>2.5 mIU/L but below upper limit of PSR	Positive	Weak recommendation, moderate-quality evidence
		<10 mIU/L but above upper limit of PSR	Negative	Weak recommendation, low-quality evidence
	Yes	Above PSR	Positive	Strong recommendation, moderate-quality evidence
		>10 mlU/L	Negative	Strong recommendation, low-quality evidence

PSR pregnancy-specific range, *TPO* thyroid peroxidase

[a] Determined by a blood test [4, 18]

nancies. Forty to fifty percent of women developed hypothyroidism at 6 weeks postpartum during follow-up. Gestational age is strongly related to the presence of subclinical hypothyroidism, and the presence of TPOAb is significantly associated with long-term thyroid dysfunction [2, 5, 8, 13–16].

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Autoimmune Diabetes Mellitus

51

Antonio Jesús Blanco-Carrasco

Abstract

Autoimmune diabetes mellitus is a chronic disease caused by the immune destruction of pancreatic beta cells. Under its classical presentation, this type of diabetes tends to cause chronic hyperglycemia, and exogenous insulin is required to survive and prevent ketosis. In genetically predisposed individuals, possibly triggered by non-well-identified factors, there is primarily a cellular (through autoreactive T cells) destruction of pancreatic beta cells. Specific biochemical assayed autoantibodies (anti-GAD65, anti-insulin, anti-IA-2, and anti-ZnT8) are the essential markers used for diagnosis. Treatment consists of daily administration of exogenous insulin under self-monitoring conditions of glucose levels. Maintenance of optimal glucose control is essential to reduce lifelong microvascular complications. Very recently, teplizumab, the first treatment with the potential to modify the course of the disease, has been approved.

Keywords

Autoimmune diabetes · Beta cell · Insulin · Autoantibodies · Anti-insulin · Anti-GAD65 · Anti-IA-2 · Anti-ZnT8

Description and Diagnosis of Diabetes as a Syndrome

The classic descriptions of diabetes mellitus (DM), especially in its symptomatic forms, have been elaborate and date back at least to the time of the Ebers Papyrus. However, the current definition and classification are descendants of much more contemporary proposals. In 1979, the National Diabetes Data Group (NDDG) of the United States proposed the nomenclature “type 1” and “type 2,” which replaced the previous classification based on the presence or absence of “dependence” on insulin. Meanwhile, the World Health Organization (WHO) included this terminology in its 1980 classification. Since then, changes have been subtle.

We could define diabetes as a group of metabolic disorders that lead to the development of hyperglycemia due to defects in insulin secretion, its action, or both. Perhaps the most relevant element is the relationship between chronic exposure to hyperglycemia and the incidence of microvascular complications. In fact, the thresholds at which an increased prevalence of these complications (especially retinopathy) has been observed constitute the values used as diagnostic criteria.

Table 51.1 provides the diagnostic values for diabetes proposed by the American Diabetes Association (ADA) and accepted internationally. Except in the context of compatible clinical findings, determinations should be repeated in the same sample or a different one. These criteria have remained

Table 51.1 Criteria for the diagnosis of diabetes [1]

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.[a]
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.[a]
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.[a]
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

DCCT Diabetes Control and Complications Trial, *FPG* fasting plasma glucose, *OGTT* oral glucose tolerance test, *NGSP* National Glycohemoglobin Standardization Program, *WHO* World Health Organization, *2-h PG* 2-h plasma glucose

[a] In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples

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unchanged since 2010. The last change involved the inclusion of glycated hemoglobin (A1C) determination as a diagnostic element once the use of a method certified by the National Glycohemoglobin Standardization Program and standardized for the Diabetes Control and Complications Trial became widespread for analysis. Previously, in 1997, we had seen the diagnostic threshold reduced from 140 mg/dL (7.8 mmol/L) to 126 mg/dL (7 mmol/L).

Etiological Classification of Diabetes

Once the biochemical diagnosis of diabetes has been made, we should establish its etiopathogenesis. In this regard, the most comprehensive classification was published by the ADA in 2014 and has not undergone significant updates (Table 51.2). However, in recent years, the concept of diabetes as a multifactorial process has emerged clearly, wherein a single individual with the disease, aspects compatible with different pathophysiological processes can manifest in combination. For example, someone may have diabetes by mixing elements compatible with autoimmunity against pancreatic islets and insulin resistance at the same time. This makes clinical management, which ideally should consider these pathophysiological aspects, not fully align with simple diagnostic labels.

Table 51.2 Diabetes mellitus classification [2]

I. Type 1 diabetes (B-cell destruction, usually leading to absolute insulin deficiency)
(a) Immune mediated
(b) Idiopathic,
II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
III. Other specific types
(A) Genetic defects of beta cell function
1. MODY 3 (chromosome 12, HNF-1α)
2. MODY 1 (chromosome 20, HNF-4α)
3. MODY 2 (chromosome 7, glucokinase)
4. Other very rare forms of MODY (e.g., MODY 4: Chromosome 13, insulin promoter factor-1)
5. Transient neonatal diabetes (most commonly ZAC/HYAMI imprinting defect on 6q24)
6. Permanent neonatal diabetes (most commonly KCNJ11 gene encoding Kir6.2 subunit of B-cell KATP Channel)
7. Mitochondrial DNA
(B) Genetic defects in insulin action
1. Type A insulin resistance
2. Leprechaunism
3. Rabson–Mendenhall syndrome
4. Lipoatrophic diabetes
5. Others
(C) Diseases of the exocrine pancreas
1. Pancreatitis
2. Trauma/pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalculous pancreatopathy
7. Others
(D) Endocrinopathies
1. Acromegaly
2. Cushing's syndrome
3. Glucagonoma
4. Pheochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Aldosteronoma
8. Others
(E) Drug or chemical induced
1. Vacor
2. Pentamidine
3. Nicotinic acid
4. Glucocorticoids
5. Thyroid hormone
6. Diazoxide
7. B-adrenergic agonists
8. Thiazides
9. Dilantin
10. y-interferon
11. Others
(F) Infections
1. Congenital rubella
2. Cytomegalovirus
3. Others
(G) Uncommon forms of immune-mediated diabetes
1. Stiff-man syndrome
2. Anti-insulin receptor antibodies
3. Others
(H) Other genetic syndromes sometimes associated with diabetes
1. Down syndrome
2. Klinefelter syndrome
3. Turner syndrome
4. Wolfram syndrome
5. Friedreich ataxia
6. Huntington chorea
7. Laurence–Moon–Biedl syndrome
8. Myotonic dystrophy
9. Porphyria
10. Prader–Willi syndrome
11. Others
IV. Gestational diabetes mellitus

Autoimmune Diabetes or Type 1A Diabetes

From Etiopathogenesis to Diagnosis

Type 1A DM (T1AD or T1D) is presented in individuals with insulin deficiency attributed to islet autoimmunity. The characterization of autoimmune diabetes development, especially at early ages, is moderately well-established. Thus, the detection of two or more autoantibodies persistently in an individual with a genetic risk or family history of T1D practically ensures the development of this disease within a period not exceeding 10 years.

The difficulty in routinely performing histological studies of the pancreas limits our ability to understand the natural history of the autoimmune process and has even led to voices advocating for a reconsideration of this direct association with autoimmunity. However, data derived from animal models, the linkage of the process to HLA, disease transfer in hematopoietic progenitor cell recipients, and disease relapses after transplantation should be sufficient to continue supporting the autoimmune origin of T1D.

The most widely accepted scientific position attributes the primary leading role in autoimmune attacks to antigen-specific autoreactive T cells. Although not performed routinely, these cells can be isolated in peripheral blood and pancreatic tissue samples from individuals with T1D. Alterations in the function of regulatory T cells also play a role. Irrefutable proof of this fact is that individuals carrying pathogenic changes in homozygosity in the AIRE gene have T1D within their spectrum of autoimmune polyglandular clinical manifestations. Another risk factor is generated by abnormalities in beta cells, such as overexpression of HLA molecules and protein misfolding, which ultimately lead to the appearance of neoantigens.

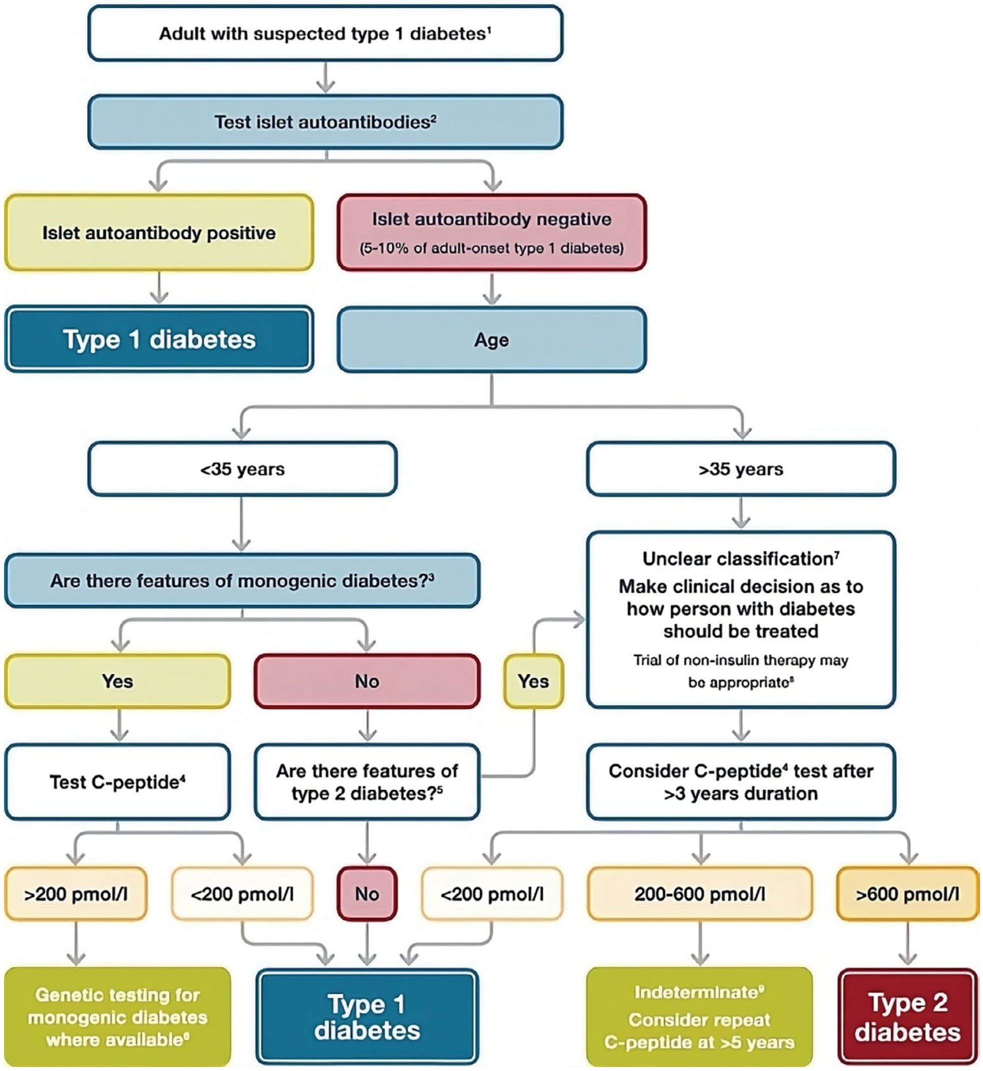
The pathogenic role of B cells is much less clear, but their involvement appears plausible. Nevertheless, the generation of autoantibodies against beta cells is crucial, as it is currently considered the cornerstone in the clinical identification and diagnosis of this condition. Although other autoantibodies have been identified, those routinely used in clinical practice include anti-GAD (glutamic acid decarboxylase), anti-IA2 (islet antigen 2), anti-insulin, and anti-ZnT8 (zinc transporter 8).

While the diagnosis of T1D in childhood typically does not raise clinical issues, we are going to explore how it becomes more challenging in adulthood. If a child presents with the classic clinical picture of diabetes (the triad of polydipsia, polyuria, and weight loss) and tests positive for any of the autoantibodies, the diagnosis of T1D is considered definitive. Even those children with negative serological studies for the usual autoantibodies (T1DB) have a genetic risk equivalent to those with a positive study (T1DA) [3]. The situation is quite different in adults, where the high prevalence of T2D makes it much more challenging. As indicated in the latest ADA/EASD consensus for managing T1D in adults [4], no single clinical feature confirms type 1 diabetes in isolation. The most discriminative feature is younger age at diagnosis (<35 years), with lower BMI (<25 kg/m^2), unintentional weight loss, ketoacidosis, and glucose >20 mmol/L (>360 mg/dL) at presentation also being informative. Other features classically associated with type 1 diabetes, such as ketosis without acidosis, osmotic symptoms, family history, or a history of autoimmune diseases are weak discriminators. Anti-GAD should be the primary antibody measured and, if negative, should be followed by anti-IA2 and/or anti-ZnT8 where these tests are available. If in a clinically highly suspicious context, immunological testing is positive, the diagnosis is also considered definitive. Conversely, if immunological testing is negative, we must consider other clinical factors and rule out other potential diagnoses (Fig. 51.1). Evaluation using GRS in this adult population with T1DB suggests that many of these diagnoses do not truly correspond to T1D [3].

Flowchart for investigation of suspected type 1 diabetes in newly diagnosed adults, based on data from White European populations:

1. No single clinical feature confirms type 1 diabetes in isolation. The most discriminative feature is younger age at diagnosis (<35 years), with lower BMI (<25 kg/m^2), unintentional weight loss, ketoacidosis, and glucose >20 mmol/L (>360 mg/ dL) at presentation also being informative. Other features classically associated with type 1 diabetes, such as ketosis without acidosis, osmotic symptoms, family history or a history of autoimmune diseases are weak discriminators.
2. GAD should be the primary antibody measured and, if negative, should be followed by islet tyrosine phosphatase 2 (IA2) and/or zinc transporter 8 (ZNT8) where these tests are available. In those diagnosed below the age of 35 years who have no clinical features of type 2 diabetes or monogenic diabetes, a negative result does not change the diagnosis of type 1 diabetes since 5–10% of people with type 1 diabetes do not have antibodies.
3. Monogenic diabetes is suggested by the presence of one or more of the following features: HbA1c < 58 mmol/mol (7.5%) at diagnosis, one parent with diabetes, features of specific monogenic cause (e.g., renal cysts, partial lipodystrophy, maternally inherited deafness, severe insulin resistance in the absence of obesity), and monogenic diabetes prediction model probability >5% (www.diabetesgenes.org/exeter-diabetes-app/ModyCalculator; accessed 20 August 2021).
4. A C-peptide test is only indicated in people receiving insulin treatment. A random sample (with concurrent glucose) within 5 h of eating can replace a formal C-peptide stimulation test in the context of classification. If the result is ≥600 pmol/L, the circumstances of testing do not matter. If the result is <600 pmol/L and the concurrent glucose is <4 mmol/L (<72 mg/ dL) or the person may have been fasting, consider repeating the test. Results showing very low levels (<80 pmol/L) do not need to be repeated. Where a person is insulin-treated, C-peptide

Fig. 51.1 Flowchart for investigation of suspected type 1 diabetes in newly diagnosed adults, based on data from White European populations [4]


Adult with suspected type 1 diabetes[1]
Test islet autoantibodies[2]
Islet autoantibody positive
Islet autoantibody negative
(5-10% of adult-onset type 1 diabetes)
Type 1 diabetes
Age
<35 years
>35 years
Are there features of monogenic diabetes?[3]
Unclear classification[7]
Make clinical decision as to how person with diabetes should be treated
Trial of non-insulin therapy may be appropriate[8]
Yes
No
Yes
Test C-peptide[4]
Are there features of type 2 diabetes?[5]
Consider C-peptide[4] test after >3 years duration
>200 pmol/l
<200 pmol/l
No
<200 pmol/l
200-600 pmol/l
>600 pmol/l
Genetic testing for monogenic diabetes where available[6]
Type 1 diabetes
Indeterminate[9]
Consider repeat C-peptide at >5 years
Type 2 diabetes

must be measured prior to insulin discontinuation to exclude severe insulin deficiency. Do not test C-peptide within 2 weeks of a hyperglycemic emergency.

5. Features of type 2 diabetes include increased BMI (≥ 25 kg/m^2), absence of weight loss, absence of ketoacidosis and less marked hyperglycemia. Less discriminatory features include non-White ethnicity, family history, longer duration and milder severity of symptoms prior to presentation, features of the metabolic syndrome and absence of a family history of autoimmunity.
6. If genetic testing does not confirm monogenic diabetes, the classification is unclear and a clinical decision should be made about treatment.
7. Type 2 diabetes should be strongly considered in older individuals. In some cases, investigation for pancreatic or other types of diabetes may be appropriate.
8. A person with possible type 1 diabetes who is not treated with insulin will require careful monitoring and education so that insulin can be rapidly initiated in the event of glycemic deterioration.
9. C-peptide values 200–600 pmol/L are usually consistent with type 1 diabetes or maturity-onset diabetes of the young (MODY) but may occur in insulin-treated type 2 diabetes, particularly in people with normal or low BMI or after long duration.

The clinical value of detecting these autoantibodies can begin even before diabetes manifests clinically. Nowadays, the existence of two presymptomatic stages is well-accepted [5]. In the first stage, seroconversion can be evident, making it possible to detect at least two different autoantibodies in peripheral blood. In stage 2, impaired insulin secretion leads to the first alterations in insulin secretion and dysglycemia that do not meet the diagnostic criteria for diabetes. The risk of progressing to T1D in the first stage is approximately 70%, while it nearly reaches 100% in stage 2 (Fig. 51.2).

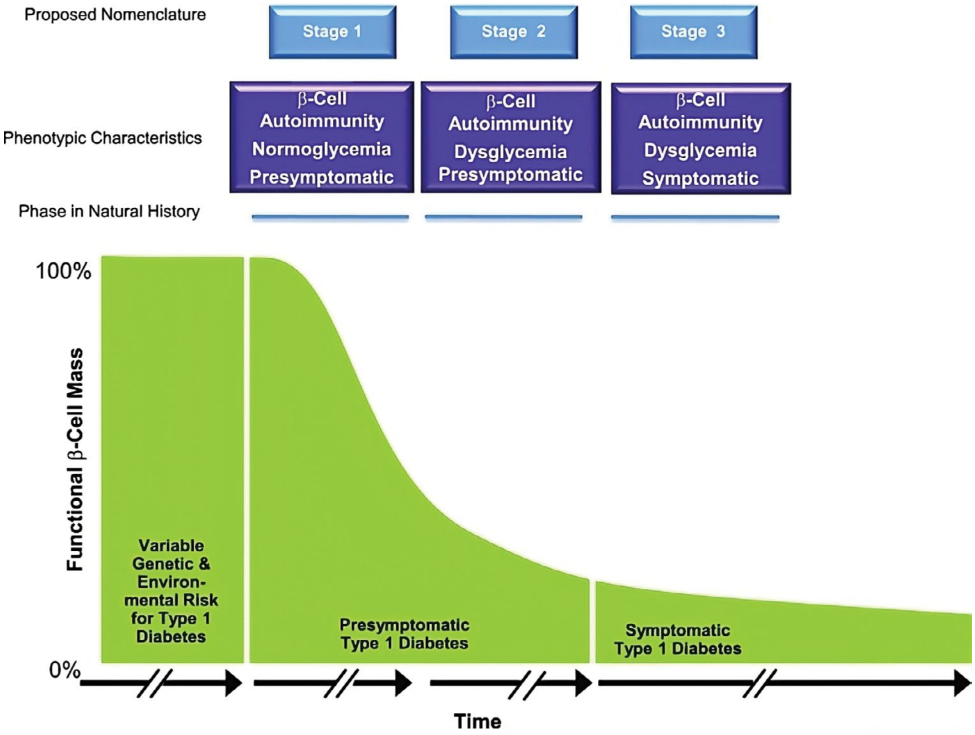

Proposed Nomenclature
Stage 1
Stage 2
Stage 3
Phenotypic Characteristics
β-Cell Autoimmunity Normoglycemia Presymptomatic
β-Cell Autoimmunity Dysglycemia Presymptomatic
β-Cell Autoimmunity Dysglycemia Symptomatic
Phase in Natural History
100%
0%
Functional β-Cell Mass
Variable Genetic & Environ-mental Risk for Type 1 Diabetes
Presymptomatic Type 1 Diabetes
Symptomatic Type 1 Diabetes
Time

Fig. 51.2 Early stages of type 1 diabetes [5]

The pathophysiology of T1D involves both environmental factors (with perhaps the highest level of evidence being the inducing role of certain viral infections) and genetic factors. Half of the heritability of the risk of developing T1D is linked to the HLA system, especially genes in class I and II. The two alleles associated with the highest risk in the Caucasian population are HLA-DR4 and HLA-DR3. Once again, this pathophysiological element has a diagnostic correlation, as HLA typing can play a fundamental role in characterizing diabetes due to its high negative predictive value. In recent years, the clinical utility of improving prediction provided by HLA has also been demonstrated by using genetic (GRS) or polygenic risk scores (PRS). These scores incorporate other genetic risk elements that, although individually carrying much less weight than HLA, collectively account for nearly the other 50% of the heritability of the risk.

The use of these tools in everyday practice is still far from being widespread. However, as early as 2018, data were published employing an original approach using information from the UK Biobank [6]. In this strategy, they defined a population of T1D as an excess of diabetes cases observed in the population with >p50 of the genetic risk score for T1D compared to the population with <p50. This unique approach revealed that 9.7% of incident cases of diabetes in a population up to 60 years old corresponded to cases of T1D, and even more surprisingly, 42% of these cases were diagnosed after the age of 30. It could be hypothesized that this genetic definition of T1D, which does not rely on serological studies, overestimates cases of adult-onset autoimmune diabetes, where type 2 Diabetes is by far the most prevalent entity. However, another study published in the same year yielded similar figures when systematically studying incident cases of diabetes in the adult population using simple clinical and biochemical variables, including the determination of anti-GAD antibodies [7].

As we have emphasized in this section, T1D is far from being a homogeneous disease, and we have already seen how its presentation in childhood and adulthood can be clearly different. In fact, in recent years, a term has been coined to highlight this heterogeneity. Thus, we speak of the existence of at least 2 different endotypes (T1DE1 and T1DE2) within autoimmune-origin diabetes [8]. They differ, among other aspects, in the typical age of onset. Their characteristics are summarized in Table 51.3.

Current Clinical Management of T1D

T1D confers the risk of acute (mainly hypoglycemia and ketoacidosis) and an array of chronic micro and macrovascular complications. Poor glycemic control, in addition to other cardiovascular risk factors and the usually unknown individual predisposition, in T1D are related to long-term damage, dysfunction, and failure of different organs. Fortunately, intensive diabetes therapy aimed at achieving near normoglycemia reduces the risk of these microvascular complications [4]. However, we have seen only a modest reduction in excess cardiovascular risk in this population, probably due to

Table 51.3 Characteristics of T1DE1 and T1DE2 [8]

Endotype	T1DE1	T1DE2
Primary genetic association	HLA DR4-DQ8	HLA DR3-DQ2
Islet autoantibodies	IAA first (<2 years old), then IA-2 with or without GAD65 autoantibodies High percentage IAA$^+$ and IAA titers at T1DM onset	GAD autoantibodies first, then with or without other autoantibodies
Other immunological findings	High percentage of islet-infiltrating CD8$^+$ T cells, high percentage of CD20$^+$ B cells	Low percentage of CD8$^+$ T cells compared with T1DE1, very low percentage of CD20$^+$ B cells compared with T1DE1
B-cell abnormalities	High proinsulin to C-peptide ratio Low percentage of insulin-containing cells Abnormal ß-cell maturation	Higher percentage of insulin-containing islets compared with T1DE1
Response to immunomodulators	Yes	Less responsive than T1DE1
Other disease associations	Coeliac disease	Thyroid autoimmunity

IAA insulin autoantibodies, *T1DE1* T1DM endotype 1, *T1DE2* T1DM endotype 2, *T1DM* type 1 diabetes mellitus

a misconception of the true magnitude of that risk and, therefore, a systematic undertreatment of classic cardiovascular risk factors [9].

It is not the purpose of this text to thoroughly review the treatment and clinical care of individuals with T1D, as this is usually carried out routinely and exclusively in endocrinology or diabetology clinics. However, for healthcare professionals not directly involved in the care of people with T1D, it is interesting to understand key aspects of treatment and self-care performed by individuals with T1D.

Firstly, we must emphasize that therapeutic education is a fundamental pillar in this process [4]. A person with T1D, whose life depends on being continuously exposed to auto-administered exogenous insulin, must make dozens, if not hundreds, of daily decisions related to their treatment. In fact, T1D is still associated with a big personal and familiar burden. Nutrition education is essential due to the prevalence of various common misconceptions, which persist even among certain healthcare professionals today. People with T1D are not obliged to avoid sugar or other carbohydrates; the most crucial aspect is the quantification of these intakes. Although there is a piece of heterogeneous evidence suggesting that low-carb diets could facilitate glycemic control [10], we should assume that individuals with T1D can consume the amount of carbohydrates they desire if they can concurrently administer a proportional insulin dose.

Currently, there are two common lines of insulin replacement: (a) The use of multiple subcutaneous insulin doses through insulin boluses, mixing the use of once-daily slow-release insulin analogs with other rapid-acting analogs before meals. (b) The use of hybrid closed-loop systems in which a semi-automated system employs only rapid-acting insulin analogs to deliver micro-doses of insulin that replace the single dose of slow-acting analogs from the previous regimen. These systems do not yet have the capacity to address hyperglycemia from unannounced carbohydrate intake, so it remains the responsibility of the patient to quantify carbohydrate intake and administer the pre-meal insulin dose, commonly known as a bolus.

These semi-automated insulin infusion systems can be considered true game-changers [11], but we must point out that their advancement has required the optimization of continuous glucose monitoring systems [12]. These latter have become the standard monitoring system in the majority of people with T1D in countries with a higher socioeconomic level. Whereas individuals with T1D previously had to perform multiple blood glucose checks through capillary blood glucose self-monitoring after finger pricking to get an approximate idea of their level of control, now people with diabetes have the option to check their interstitial glucose levels by consulting the information updated every 1–5 min by the subcutaneous sensor they have inserted, depending on the models. For people on multiple doses, analyzing this information is crucial. Additionally, in automated systems, this input, along with various predictive systems for its future evolution, is used to determine the insulin dose to be administered.

Prevention of Beta-Cell Destruction

Prevention of beta-cell destruction at primary (to prevent the development of autoimmunity), secondary (to prevent beta-cell destruction), and tertiary (after the onset of DM) levels would be a desirable alternative to reduce burden of treatment with insulin. Unfortunately, there is currently no treatment with this objective approved in Europe. Recently, the FDA has given approval to teplizumab, an anti-CD3 monoclonal antibody. Treatment with this drug has been shown to significantly delay the diagnosis of T1D in individuals in presymptomatic stage 2, i.e., with positive immunology and dysglycemia [13].

Latent Autoimmune Diabetes of Adulthood

Controversy remains as to whether latent autoimmune diabetes of adulthood (LADA) is another discrete subtype, a slower progressive form of type 1 diabetes, or a mixture of individuals with different types of diabetes or even a combination of varied characteristics in the same subject [14].

Insulin-Dependent Diabetes Induced with Checkpoint Inhibitors

An emerging and very clinically relevant issue is the development of nearly complete insulin deficiency associated with the treatments with immune checkpoint inhibitors, which may present with hyperglycemia and even diabetic ketoacidosis. Forty percent have at least one positive autoantibody, and there is a clear predominance of HLA-DR4, which is present in more than 75% of affected subjects. Other immune adverse events were seen in 70%, and endocrine adverse events were seen in 44% [15].

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52

Autoimmune Adrenalitis

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Abstract

Addison's disease (AD) is the most common cause of primary adrenal insufficiency, and it is characterized by deficient production of glucocorticoids and/or mineralocorticoids by adrenals. The symptoms and signs of adrenal insufficiency vary from nausea, vomiting, anorexia, and abdominal pain to fever, weakness, fatigue, lethargy, and confusion, while coma may also appear. Shock not responsive to volume may also occur. The most common cause of AD is autoimmune adrenalitis. It is linked to high titers of cortex adrenal autoantibodies (ACA). In this chapter, the authors review the clinical and laboratory and summarize the diagnostic criteria of AD. In addition, some aspects of treatment are discussed.

Keywords

Addison's disease · Adrenal · Adrenal insufficiency · Diagnostic criteria · Adrenalitis

Addison's disease is the most common cause of primary adrenal insufficiency, and it is characterized by deficient production of glucocorticoids and/or mineralocorticoids by adrenals. Herein, we will focus only on Autoimmune Addison's disease (AAD), an idiopathic autoimmune disease with autoantibodies and autoreactive T cells against the adrenal tissue.

History and Epidemiology

The adrenal gland was first described in 1552 by Bartolomeu Estaquio as the "Glandulae renis incumbents" in Opuscula Anatômica [1], although its function remained a mystery for centuries. However, the puzzle began to be solved in 1885 when Thomas Addison described the clinical features of 11 patients with primary adrenal insufficiency [2]. In 1949, cortisone synthesis allowed this condition to be treated [3].

Addison's disease is a rare disorder with an incidence of 4:1,000,000 per year in Western societies [4]. However, it is more common than 30 years ago because its prevalence in the general population is now more than three times higher than in 1970 [5]. Patients with isolated AAD are predominately male (70%) during the first two decades of life, there is no predominance during the third decade, and are predominately female (81%) after that. On the other hand, when AAD is part of polyglandular autoimmune syndromes, the patients are mainly female (70%) [6]. Primary adrenal insufficiency is clinically evident in 1 in 8000 individuals in Western countries [7], and AAD is the most common cause in these territories, accounting for 68–94% of cases in the different studies [6]. Long-term health-related quality of life is significantly impaired in patients with Addison's disease, even with treatment. Still, it is inversely related to the delay in establishing the diagnosis after disease onset [8], emphasizing the importance of recognizing the disease early.

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Pathogenesis

Humoral and cellular immunity plays a role in the pathogenesis of AAD. Autoantibodies will be described in a separate item. Concerning cellular immunity, decreased suppressor T-cell function and increased circulating Ia-positive T cells have been described in AAD patients [9, 10]. In addition, genetic susceptibility has an association with HLA B8, DR3, and DR4 alleles, except in cases of polyglandular syndrome, in which no HLA has been found [11].

Clinical Manifestations

Addison's disease is the final result of AAD; the initial phase is subclinical, and after at least 90% of the adrenal gland has been destroyed, symptoms of adrenal failure appear [12]. The symptoms and signs of adrenal insufficiency depend upon the rate and extent of loss of adrenal function. In the acute scenario, nausea, vomiting, anorexia, abdominal pain, fever, weakness, fatigue, lethargy, confusion, and coma may appear. Shock not responsive to volume is a typical finding. An adrenal crisis in an adult is defined as an acute deterioration in health status associated with absolute hypotension (systolic blood pressure < 100 mm Hg) or relative hypotension (systolic blood pressure ≥ 20 mm Hg lower than usual), with features that resolve within 1–2 h after parenteral glucocorticoid administration (a marked resolution of hypotension within 1 h and improvement in clinical symptoms over 2 h) [13].

During chronic disease, the main finding is fatigue, and patients also present weakness, lack of stamina, and weight loss. Gastrointestinal problems are also frequent, including nausea and abdominal pain, possibly related to a loss of gut mobility. Dizziness, irritability, and postural hypotension are also frequent complaints; patients may survive without a diagnosis for many years until a minor infection leads to cardiovascular collapse. Hyperpigmentation and salt-craving are highly specific to primary adrenal insufficiency. Most patients have the clinical findings described in Table 52.1.

Pathological Features

The adrenal glands are invariably small, in contrast to tuberculosis or neoplasias. Histopathologically, there is a widespread mononuclear cell infiltrate in the active phase with lymphocytes, plasma cells, and macrophages. The standard three-layer histological structure is not more evident, and the adrenocortical cells' pleomorphism and necrosis can be observed [15]. Later, fibrous tissue can replace the cortex.

Laboratory Features

Hyponatremia is described in 85–90% of AAD patients, but it is usually less pronounced than in secondary adrenal failure [14, 15]. Hyperkalemia is reported in approximately 65% of AAD patients [16]. Table 52.2 presents a summary of laboratory findings in AAD. Levels of cortisol, measured between 8:00 and 9:00 am, less than 3 µg/dL confirm the diagnosis of adrenal insufficiency. On the other hand, levels ≥19 µg/dL exclude this diagnosis. Levels between 3 and 19 µg/dL need additional tests. Alternatively, a short ACTH stimulation test can be performed using intravenous 250 µg synthetic ACTH. If after 30 or 60 min of this injection, there is an increase in serum cortisol level to a peak of less than 18 mcg/dL (500 nmol/L), the diagnosis of adrenal insufficiency is established [17] (Table 52.3).

Table 52.1 Clinical manifestations of Addison's disease

Weakness and fatigue
Anorexia
Loss of weight
Dehydration
Hypotension and tachycardia
Abdominal pain or cramps
Nausea, vomiting
Diarrhea
Salt craving
Postural symptoms
Skin or mucosal hyperpigmentation
Listlessness
Amenorrhea and reduced libido

Table 52.2 Laboratorial and image findings in Addison's disease

Hypoglycemia
Hyponatremia
Hyperkalemia
Increasing of BUN and creatinine
Hypercalcemia
Mild acidosis
Normocytic and normochromic anemia
Neutropenia, lymphocytosis, and eosinophilia
Low cortisol levels
High ACTH levels
Compute tomography or magnetic resonance image with adrenal alterations

Table 52.3 Proposed diagnostic criteria for autoimmune Addison's disease

1. Basal cortisol <3 µg/dL (83 nmol/L) and/or ACTH >100 pg/mL (22 pmol/L), at 8:00–9:00 am *Or* Short ACTH stimulation test with 250 µg IV leading a rise in serum cortisol level after 30 or 60 min to a peak less of 18 mcg/dL (500 nmol/L)
2. Normal or reduced adrenal gland volume on computerized tomography (CT) and MRI and without abdominal X-ray or CT calcifications.
3. Anti-cortex adrenal antibodies or high titers of anti-21-hydroxylase antibodies
4. Exclusion of other causes of primary adrenal insufficiency: Genetic (clinical signs or symptoms: Achalasia, alacrimia, deafness, or hypogonadotropic hypogonadism in males or genotyping); adrenoleukodystrophy (levels of very long chain fatty acids within normal range); infectious diseases (tuberculosis, paracoccidiomycosis, histoplasmosis, HIV, CMV); drugs (mitotane, ketoconazole, rifampin, etc.); adrenal hemorrhage or thrombosis; neoplasias; infiltrative (sarcoidosis, amyloidosis, hemochromatosis).
5. Other(s) concomitant autoimmune condition(s) (Hashimoto's thyroiditis, pernicious anemia, rheumatological autoimmune disease, autoimmune hemocytopenia, and others)

Definitive diagnosis 1, 2, 3, and 4;
Probable diagnosis 1, 2, 4, and 5

Autoantibodies

The presence of high titers of cortex adrenal autoantibodies (ACA), detected by indirect immunofluorescence on cryostatic sections of adrenal glands, has been used for many years because it is the best marker for identifying AAD [6]. These antibodies react against all three zones of the adrenal cortex. Low titers of ACA have been described in unequivocal posttuberculosis adrenalitis. More recently, the identification of the enzyme steroid-21-hydroxylase as the antigen allowed the development of highly sensitive and specific radio-binding assays for steroid-21-hydroxylase (CYP21A2 or P450c21) autoantibodies detection [18]. The antigen targets are the steroidogenic enzymes: P450scc (CYP11A1, side-chain cleavage enzyme), P450c17 (CYP17, 17-alpha-hydroxylase), and P450c21 (CYP21A2, 21-hydroxylase). These antibodies may be present in 80% of the cases [5]. Antiadrenal antibodies are more common in women and people with autoimmune disorders. Among adult patients with autoimmune diseases who have these autoantibodies, 21% developed overt adrenal insufficiency and 29% subclinical adrenal insufficiency after a follow-up of 45 months [17], with a higher risk of progression among children [18]. The presence of ACA in polyglandular autoimmune syndrome type 1 patients has a predictive value for the development of 92% in this population.

Diagnostic Criteria

First, it is necessary to diagnose adrenal insufficiency. It is shortly performed when basal serum cortisol is lower than 3 µg/dL (83 nmol/L) and/or ACTH is higher than 100 pg/mL (22 pmol/L), obtained in the interval between 8:00 and 9:00 am. Alternatively, a short ACTH stimulation test can be performed using intravenous 250 µg synthetic ACTH. If after 30 or 60 min of this injection, there is an increasing serum cortisol level to a peak of less than 18 mcg/dL (500 nmol/L), the diagnosis of adrenal insufficiency is established (Table 52.3).

The second step is to define the autoimmune nature of the process; however, no diagnostic criteria are currently available. We suggest in this chapter some elements that can lead to AAD diagnosis. The main goal of the differential diagnosis is to exclude secondary conditions that can cause adrenal insufficiency, such as tuberculosis, HIV, drugs, and genetic disorders. After excluding these conditions, it is essential to image the adrenal glands; observation of an enlarged gland makes an autoimmune diagnosis less probable. Conversely, the presence of autoantibodies in the adrenal tissue or against steroid enzymes confirms the autoimmune adrenal insufficiency diagnosis. Alternatively, the probable diagnosis can also be supported in the absence of these antibodies and with concomitant autoimmune conditions (Table 52.3).

Differential Diagnosis

Certain conditions may mimic adrenal insufficiency shock, such as sepsis, hypovolemia, cardiogenic shock, exogenous intoxication, hyperkalemia from renal failure, and abdominal pain from porphyria. Malignancy is an important differential diagnosis among those patients presenting with gastrointestinal complaints and weight loss. Clinical conditions that induce hyperpigmentation (antimalarial, antineoplastic, tetracyclines, phenothiazines, zidovudine, hemochromatosis, porphyria cutanea tarda, heavy metals) should also be excluded. AAD can be part of autoimmune polyglandular syndromes (APS) types 1 and 2. The first one is characterized by patients having at least two conditions of the triad, including chronic mucocutaneous candidiasis, hypoparathyroidism, or Addison's disease, and APS type 2 (Schmidt's syndrome), represented by individuals with Addison's disease and autoimmune thyroid disease and/or diabetes mellitus type 1 but no hypoparathyroidism or candidiasis.

The approach used to identify the cause of primary adrenal insufficiency depends on the history of the patient and the presence of associated disorders. Abdominal CT should be performed, and AAD can be excluded in the presence of an enlarged adrenal gland and calcifications. In young men, particularly in boys younger than 15 years of age, adrenoleukodystrophy must be excluded, even in the absence of neurologic symptoms.

Treatment

The standard initial therapy is corticosteroid replacement. Treatment should not be delayed during an acute crisis to perform diagnostic studies or await laboratory results. Hydrocortisone should be given as 100 mg bolus followed by 200 mg every 24 h administered as a continuous infusion or as 50 mg intravenous boluses every 6 h [13] with physiological saline (1 L during the first hour is appropriate in most cases) to all patients for whom there is strong clinical suspicion of AAD. Alternatively, 4 mg dexamethasone every 12 h could be administered; dexamethasone cannot affect cortisol assays. Correcting hemodynamical and metabolic disturbs with large volumes of intravenous saline and glucose is mandatory. Look for precipitating factors, and modification is advised, especially infections.

The maintenance treatment is done by the use of oral hydrocortisone 15–25 mg a day, with 15–20 mg in the morning and 5–10 mg at 4–6 pm, or cortisone acetate 20–35 mg a day in two or three divided doses per day, with the highest dose given in the morning at awakening [16]. The superiority of a regimen of three times daily compared to two times daily was suggested in one study but remains unclear [14]. Daily cortisol secretion is between 5 and 10 mg/m^2 of the body surface area. This dose is equivalent to administering 15–25 mg of hydrocortisone or 25–37.5 mg of cortisone acetate. Because excess glucocorticoid may decrease bone mineral density, we suggest using the lowest glucocorticoid dose that relieves symptoms. Mineralocorticoid replacement is accomplished using fluorohydrocortisone (florinef, 0.05–0.2 mg daily). Hypertension, bradycardia, suppressed renin levels, and a retarded growth rate are clinical signs of over-treatment with mineralocorticoids; this reposition is usually not necessary when high doses of cortisol are used. However, cortisol should be given if a synthetic glucocorticoid (prednisolone or dexamethasone) is used when the cortisol dose has been tapered to near-maintenance levels. Weight, blood pressure, and electrolytes should be checked periodically.

Education regarding the disease and using a personal card, bracelet/necklace containing the diagnosis are strongly recommended for all patients with adrenal insufficiency. Additionally, during stressful periods, increasing the cortisol dosage to two to three times the usual daily dose for 3 days is strongly recommended for all patients [16]; patients who are about to undergo surgery also need to adjust their glucocorticoid dose. For major surgeries, administering intravenous hydrocortisone 100 mg/m^2 per day is necessary for 24 h perioperatively before tapering over several days to a maintenance dose. Patients should also be advised to learn when and how to inject dexamethasone or hydrocortisone during emergencies.

Prognosis

The survival rate of patients adequately diagnosed and treated is similar to that of the normal population. Before steroid replacement therapy, the survival rate was usually 2 years or less. Although spontaneous recovery of adrenal function has been described in AAD [19], one study reported that the occurrence was rare [20, 21].

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53

Autoimmune Hypophysitis

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Abstract

Autoimmune hypophysitis is due to an immune-mediated inflammation of pituitary gland. It is also known as lymphocytic hypophysitis and causes pituitary tissue damage with initial pituitary enlargement that can evolve to remission, for spontaneous or pharmacological resolution of the inflammation, or evolve to progressive diffuse destruction with gland atrophy and various degrees of pituitary dysfunction. During the last decades, the spectrum of forms of hypophysitis has broaden, and now, we also recognize granulomatous hypophysitis, xanthomatous hypophysitis, IgG4-related hypophysitis, immune checkpoint inhibitors-induced hypophysitis and other very rare forms.

The autoimmune process against the pituitary gland is made evident by the appearance of circulating antipituitary autoantibodies (APA), mainly detected by indirect immunofluorescence on cryostatic sections of human or primate pituitary. Several putative target autoantigens have been identified, but the low diagnostic sensitivity and specificity of APA for autoimmune hypophysitis strongly limit the clinical use of their detection.

Hypophysitis should always be considered in the differential diagnosis of non-secreting space-occupying lesions of sella turcica.

Keywords

Adrenal insufficiency · Anti-pituitary autoantibodies · Hypopituitarism · IgG4 hypophysitis · Immune checkpoint inhibitors · Lymphocytic hypophysitis

Hypophysitis is a general term used to describe sellar and/or suprasellar inflammations that result in structural modifications of hypothalamus and/or pituitary gland and may be associated with anterior and/or posterior pituitary hormonal deficiencies [1]. The most common form of hypophysitis is thought to be lymphocytic hypophysitis (Ly-H). It is also commonly referred to as "autoimmune hypophysitis" (AH) because its epidemiological, histomorphological and clinical features are suggestive for an autoimmune pathogenesis. Indeed, most of cases of hypophysitis have an autoimmune etiology [1], but during the last decade, additional pathogenetic mechanisms have been unraveled, and hypophysitis is now considered a heterogeneous entity that may be caused by autoimmune, inflammatory, infectious, neoplastic or idiopathic disorders [1]. The flogistic destruction of the pituitary gland can be self-limiting or result in permanent endocrine/neurological dysfunction. Accordingly, the clinic manifestations of hypophysitis can range from an asymptomatic to a rapidly progressive disease and, in some cases, even with potentially life-threatening complications.

Epidemiological data are scarce and imprecise, also because of the different denominations in the literature and a complex classification of this disease. Nevertheless, hypophysitis is considered a rare condition, with an estimated prevalence of approximately 1 in 9 million/year [1], which is probably underestimated. The original work by Caturegli et al. [1] was derived from a very limited number of biopsy-proven cases of hypophysitis over 15 years from a single center. That work was limited by the fact that only LyH and granulocytic forms were included. The increased detection of several novel forms of hypophysitis over the past decade has dramatically changed the landscape of hypophysitis. More specifically, two newly described forms of hypophysi-

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tis such as immune checkpoint inhibitor (ICI)-induced hypophysitis (ICI-H) and IgG4 hypophysitis (IgG4-H) are responsible for an increase in cases reported in the literature. In addition, other forms, namely isolated adrenocorticotropic hormone (ACTH) deficiency and anti-pituitary-specific transcription factor-1 hypophysitis, have been recently identified [2]. To date, the overall prevalence of hypophysitis is estimated at 0.2–0.88% [1, 3].

Clinical Manifestations

Clinical manifestation of hypophysitis is widely variable, ranging from clinically asymptomatic to being characterized by one or more features of hypopituitarism or by pituitary apoplexy with, rarely, rapid death from circulatory collapse and adrenal crisis. Clinical findings are caused by four major causes: pituitary enlargement, anterior pituitary defects, infundibulum/posterior pituitary defect and stalk impairment. The majority of patients present with symptoms related to compressive and inflammatory effects of enlarged pituitary on sellar and parasellar structures, such as headache (due to distension of dura madre), which is present in over 50% of cases at diagnosis, visual field and acuity reduction (due to compression of optic chiasm) and/or, more rarely, cranial nerves palsy (due to expansion in cavernous sinus). Anterior hypopituitarism has been reported in literature in 40–81% of patients with hypophysitis [4]. Differently from pituitary adenomas, hyperprolactinemia does not occur frequently and may be more often secondary to stalk compression, impaired dopamine effect for inflammation, immunological destruction of lactotrophs with PRL release, or supposed PRL-secretion stimulating autoantibodies [2]. Interestingly, secondary hypothyroidism and secondary hypocortisolism are frequently reported. Indeed, in hypophysitis, ACTH deficiency is the most frequently observed deficiency, followed by LH/FSH and TSH deficiencies, different than what observed with other causes of panhypopituitarism. Central AI has been reported in 20–75% of patients and the difference with other causes of hypopituitarism is more profound in cases of ICI-H [5]. Furthermore, hypernatremia from isolated ACTH deficiency is observed in patients in PD1/PDL1 inhibitor therapy [6]. The rapid identification of signs and symptoms of ACTH deficiency is essential and may be more difficult in cases of ICI-H, because of the overlap with the symptoms of the underlying tumor [5]. When hypophysitis occurs in children, GH deficiency can cause slow growth and short stature.

Symptoms related to diabetes insipidus, reported with an overall frequency that varies from 20% to 48% [7], are constantly present in lymphocytic infundibuloneurohypophysitis (LyIN-H) and lymphocytic panhypophysitis (LyP-H), due to direct infundibulo-neurohypophyseal damage, but can also occur in lymphocytic adenohypophysitis (LyA-H) as a consequence of stalk compression and impaired vasopressin transport. The coexistence of other autoimmune diseases is reported consistently at about 25% of cases [1].

Diagnostic Criteria and Treatment

Diagnosis of hypophysitis and of its underlying causes remains challenging. A delay in diagnosis is often observed due to misinterpretation of clinical signs and symptoms and of imaging data. A rapid diagnosis is however critical, mainly because secondary adrenal insufficiency is a life threatening condition. The diagnostic approach of hypophysitis comprises: (a) hormonal and biochemical analyses, (b) imaging evaluation and (c) identification of secondary causes of hypophysitis.

As for the case with pituitary incidentalomas, hormonal evaluation must always include: prolactin, cortisol, FT4, TSH, IGF-1 and, in males, FSH, LH and testosterone. Evaluation of FSH, LH and estradiol in women should be reserved to subjects in fertile age with menstrual irregularities. The routine determination of GH and ACTH is generally less relevant, because a reduced concentration of IGF-1 or cortisol are essential for a diagnosis of hormonal deficit. As for cortisol, morning concentrations below 3 mcg/dL are diagnostic for adrenal insufficiency, while, in the setting of a suspected hypophysitis, the diagnosis may be excluded only for concentrations higher than 15 mcg/dL. An ACTH stimulation test (either with 1 mcg or with 250 mcg) is often needed to exclude an underlying adrenal insufficiency. It is noteworthy that treatment with hydrocortisone [8] must never be delayed in the presence of clinical signs or symptoms strongly suggesting adrenal insufficiency, even if hormonal data are not yet available. Secondary hypothyroidism is made evident by low free thyroxine concentrations in the presence of a TSH that can be low, normal or only slightly elevated. Similarly, in males, a low morning serum testosterone along with low or normal gonadotropins indicated hypogonadotropic hypogonadism. Even though IGF-1 is normally included in the routine screening analyses, only stimulation tests (such as GHRH+arginine or insulin tolerance test) may clearly document a GH deficiency. In the presence of polyuria (defined as >50 mL/kg/24 h in adults), high serum sodium (>145 mmol/L) and high plasma osmolality (≥300 mosm/kg) or copeptin levels below 2.6 pmol/L, in the presence of normal serum sodium and plasma osmolality, make the diagnosis of central diabetes insipidus [9]. In the case of an undeterminate diagnosis with the basal serum analyses, a hypertonic saline infusion test (rather than the classical water deprivation test) is needed to rule out the disease [9]. Recently, an arginine infusion test has been proposed as alternative dynamic test [10]: a copeptin concentration below 3.8 pM at 60′ post-infusion of 0.5 g/kg arginine would allow a diagnosis of central diabetes insipidus.

Pathologic MRI signs may be observed in up to 98% of patients with Ly-H and 77% of ICI-H cases [5]. The most common MRI findings include pituitary enlargement, pituitary stalk thickening, pituitary contrast enhancement, suprasellar extension and loss of posterior pituitary bright spot on T1-weighted imaging [4]. Parasellar extension, apoplexy, "figure of 8" appearance or the presence of a "dural/meningeal tail" (caused by inflammation of the dura mater) are less common findings. Most challenging is the diagnostic differentiation of a globous enlarged pituitary because of hypophysitis from a pituitary macroadenoma. Pituitary biopsy remains the gold standard for the final diagnosis of hypophysitis. However, this is an invasive and potentially dangerous approach and should be reserved only to those cases in which the diagnosis remains uncertain and the management would change significantly with the correct diagnosis. According to a radiological score proposed by Gutenberg et al. [11], a diagnosis of hypophysitis would be favored by: onset during the early post-partum period or late pregnancy, absence of the posterior pituitary "bright spot," homogeneous uptake of gadolinium contrast and higher enhancement post-contrast and a pituitary stalk thickening. Additional analyses may include immunoglobulin levels if a IgG4-related disease is suspected or quantiferon testing, ANCA antibodies or serum angiotensin converting enzyme, to rule out granulomatous inflammation or vasculitis. The role of pituitary autoantibodies in routine practice remains elusive (see detail in the subsequent paragraph of Ly-H).

No clear consensus in the treatment of hypophysitis is available. Therapy consists mainly of hormonal substitutive treatment and treatment of neurological and mass effects. Corticosteroid treatment (e.g., prednisone 1 mg/kg/day), alone or in combination with other immunosuppressive agents, is normally utilized in the case of rapid onset of neurological symptoms and mass effects due to the enlargement of the pituitary gland. Surgery and stereotactic radiotherapy are to be reserved to selected cases mainly in the cases of rapid progression of neurological symptoms and large space-occupying lesions, especially if in the presence of an uncertain diagnosis. Surgery is a preferred option in the case of granulomatous hypophysitis.

Classification of Forms of Hypophysitis

Lymphocytic Hypophysitis

Ly-H (Table 53.1) is the most frequent form of hypophysitis. Some reports indicated that Ly-H would represent around 71.8% of all cases of hypophysitis [1]. However a wide range of frequency ranging from 55% to 86% of all cases of

Table 53.1 Different forms of hypophysitis

Forms	Frequency among hypophysitis cases	Gender distribution	Notes
Lymphocytic (Ly-H)	55–86%	F/M ratio = 4:1	Autoimmune origin. Presence of circulating autoAb, lymphocytic infiltration. Associated with pregnancy and the peri-partum period.
Granulomatous (G-H)	≅20%	F/M ratio = 2.6:1	Late manifestation of Ly-H.
Xanthomatous (X-H)	≅3%	F/M ratio = 3:1	Local inflammatory response to a ruptured Rathke's cleft cyst.
IgG4-related (IgG4-H)	≥4%	Isolated IgG4-H more common in females	Associated with systemic IgG4-disease or isolated IgG4-H. Elevated serum IgG4 antibody levels. Infiltration with ≥10 IgG4-positive plasma cells per high power field.
ICI-induced	11–13.6% of CTL4-inhibitors receivers 0.5% of PD1/PDL1 inhibitors receivers	F/M ratio = 1:4	A combination of type II and type IV hypersensitivity reactions as a likely pathogenetic mechanism.
Other rare forms	≤1%	Undetermined	Include necrotizing hypophysitis, anti-PIT1 hypophysitis, acquired isolated ACTH deficiency or secondary forms (sarcoidosis, infections, proliferative disorders and tumors).

autoAb autoantibodies, *ICI* Immune checkpoint inhibitors hypophysitis has been reported [4]. Ly-H may affect anterior (Lymphocytic Adenohypophysitis, LyA-H), posterior (Lymphocytic Infundibuloneurohypophysitis, LyIN-H) or both (Lymphocytic Panhypophysitis, LyP-H) pituitary lobes. Mean age is third–fourth decades. No strict female predisposition is reported for LyIN-H and LyP-H, though a weak female predisposition has been reported for LyP-H. LyA-H is more common in women and has an established, strong association with late pregnancy and postpartum (from 30% to 70% of cases). This association can be explained by the increase in pituitary antigens secondary to the pituitary hyperplasia that occurs during pregnancy and the change in the hypophyseal blood flow pattern, with subsequent increasing exposure to the immune system. Furthermore, molecular mimicry through co-expression of antigens such as enolase isoforms in both pituitary and placenta can also explain the increased frequency of LyA-H during pregnancy. A diagnosis of Ly-H does not necessarily impact on pregnancy outcomes. Ly-H may occur in one pregnancy and resolve in a subsequent one.

Histological examination with immuno-histochemistry shows polyclonal lympho-plasmacytic infiltrate, with plasma cells, rarely eosinophils and occasionally neutrophils and macrophages; aspects of focal or diffuse destruction of glandular acines and evolution to fibrosis are common [1]. Mast-Zellen and folliculo-stellate cells, with lymphocytes-chemotactic and antigen-presenting role, have also been described, supporting the role of immune response. Documented neurohypophyseal, infundibular or pituitary stalk tissue involvement is reported with varying frequency (20–62%; ref. [1]).

Autoantibodies have been detected in patients with Ly-H, though their pathogenetic role remains elusive. The most widely used method to detect anti-pituitary autoantibodies (APA) is indirect immunofluorescence on cryostatic sections of human or primate pituitary. A specific pattern of immunofluorescence, namely Type 1 isolated pituitary cells, seems to be more predictive of autoimmune hypophysitis than Type 2 all pituitary cells [12]. However, the clinical use of this assay type is strongly limited by a low diagnostic sensitivity and a low diagnostic specificity. Prolactin cell-specific autoantibodies were initially identified [13]. Subsequently, ACTH cell-specific autoantibodies were also demonstrated, especially in patients with Cushing's disease or isolated ACTH deficiency, with aspartic protease as a candidate autoantigen [14]. GH-secreting cell autoantibodies have been detected in some patients with Turner's syndrome, partial GH deficiency or idiopathic GH deficiency. α-Enolase was the first identified pituitary autoantigen recognized by human autoantibodies [15]. However, α-enolase is widely expressed in several human tissues and α-enolase autoantibodies have a very low diagnostic specificity for Ly-H. Also gamma-enolase has been recognized as a target of pituitary autoantibodies. Interestingly, gamma-enolase is expressed in both the pituitary and the placenta, thus providing a theoretical basis for the strong association between pituitary autoimmunity and pregnancy. The use of radioligand binding assays has shown the presence of autoantibodies against GH, pituitary gland specific factor 1a (PGSF1a) and/or pituitary gland specific factor 1b (PGSF1b) in 18% of lymphocytic hypophysitis patients with gland enlargement and in 36% of Ly-H patients with no pituitary enlargement, as well as in 10% of patients with other autoimmune diseases [16]. Other pituitary autoantigens include secretogranin 2, TPIT and chorionic somatomammotropin. Anti-rabphilin 3A antibodies have been shown to be positive in cases of autoimmune diabetes insipidus [17]. At present, the clinical applicability of these immune markers in the routine diagnosis and management of patients with Ly-H remains limited because of a very low diagnostic sensitivity and specificity and conflicting results generated by different methods.

Granulomatous Hypophysitis

Several granulomatous conditions such as tuberculosis, sarcoidosis, granulomatosis with polyangiitis, Langerhans histiocytosis, syphilis and ruptured Rathke's cleft cyst may cause secondary hypophysitis. These forms may apparently resemble the so-called granulomatous hypophysitis (G-H) (Table 53.1), which occurs in approximately 20% of hypophysitis cases. However, G-H appears to be more related to Ly-H. Accordingly, this form is considered the second more common primary (autoimmune) form of hypophysitis. Indeed, similarly to Ly-H, G-H is more frequent among females, but does not show a significant association with pregnancy or the peri-partum period. Furthermore, the mean age of appearance is around 8 years higher than that of Ly-H. Histopathology of G-H shows infiltration by numerous histiocytes, that may be arranged as granulomas, together with lymphocytes, multinucleated giant cells and fibrosis. In some cases, G-H and Ly-H seem to coexist in the same individual. Even though the precise nature of this form of hypophysitis is not fully understood, several lines of evidence indicate that G-H might represent a late manifestation of Ly-H.

Xanthomatous Hypophysitis

Xanthomatous hypophysitis (X-H) (Table 53.1) is a rare form of primary hypophysitis, characterized by the presence of foamy macrophages in the pituitary gland. It is more common in women, but does not show any relation with pregnancy or the post-partum period. Central diabetes insipidus is not a common manifestation of X-H. Typically, MRI often shows cystic areas of liquefaction within the pituitary. Potential causes of this form of hypophysitis include autoimmunity, infection or regional endothelial dysfunction, but the most likely etiology is a local inflammatory response to a ruptured Rathke's cleft cyst.

IgG4-Hypophysitis

IgG4-hypophysitis (IgG4-H) (Table 53.1) is a recently identified form, also known as plasmacytic hypophysitis. This form of hypophysitis is often part of a systemic, multiorgan IgG4-related disease [18], that may comprise several different conditions, among which Riedel's thyroiditis, autoimmune pancreatitis, retroperitoneal fibrosis, Mikulicz's disease, or inflammatory pseudotumor. IgG4-H was histologically documented for the first time in 2007 and is more common in males. However, the isolated form, without other systemic manifestations, is more common in females. It is considered a very rare condition, but, in recent studies, several cases previously diagnosed as Ly-H were reclassified as IgG4-related. Diagnosis is made by the combinations of several criteria [19], such as a) biopsy-proven IgG4 disease of the pituitary gland or b) positive imaging features of hypophysitis with biopsy-proven IgG4 disease of other organs, if no pituitary biopsy is available or c) imaging evidence of hypophysitis, with elevated serum IgG4 antibody levels (>140 mg/dL) and prompt response to glucocorticoid therapy when neither the biopsy samples of pituitary nor of other sites are available. At histopathologic analysis, mononuclear infiltration with ≥10 IgG4-positive plasma cells per high power field, storiform fibrosis and rarely lymphoid follicles and eosinophils are detected. This form of hypophysitis is responsive to glucocorticoid therapy, hence the need for a rapid and correct diagnosis.

Immune Checkpoint Inhibitor-Induced Hypophysitis

ICIs therapy in oncology is based on the use of monoclonal antibodies binding to, and inhibiting, the action of cytotoxic T-lymphocyte antigen 4 (CTLA4) and programmed cell death 1 (PD1) on T lymphocytes, as well as PD1 ligand 1 (PDL1) on antigen-presenting cells. Among adverse effects of ICIs therapy are endocrinopathies, which also include secondary hypophysitis. ICI-H is more common in males than in females (approximately 79%, male: female ratio: 4:1). The prevalence of hypophysitis is 11–13.6% among patients receiving the CTL4-inhibitor ipilimumab for metastatic tumor, but is lower among patients receiving PD1/PDL1 inhibitors such as pembrolizumab or nivolumab [20]. In addition, treatment with CTLA4 inhibitors is associated with a more rapid development of hypophysitis as compared to treatment with PD1/PDL1 inhibitors (9.3 weeks vs. 25.8 weeks, respectively) [20]. Even though the pathophysiology of ICI-H is not completely elucidated, histopathological analysis have revealed a combination of type II and type IV hypersensitivity reactions as a likely mechanism [8]. CTL4 inhibitors are IgG1/IgG2 and may more likely trigger an antibody-mediated cytotoxicity or the classic complement pathway on the surface of pituitary cells, as compared to PD1/PDL1 inhibitors which are IgG4 monoclonal antibodies. Interestingly, PD1/PDL1 inhibitor therapy may often cause isolated ACTH deficiency, with secondary adrenal insufficiency and hyponatremia, without typical features of hypophysitis at MRI scans.

Other Forms of Hypophysitis

Necrotizing hypophysitis is the among the rarest forms of primary hypophysitis. It is more frequent among females than among males. Pathogenesis is unknown, but it is believed that this form may represent a more severe manifestation of other forms of hypophysitis (including ICI-H). It is clinically characterized by symptoms of mass effect with visual impairment, eye pain and aseptic meningitis. Several inflammatory conditions such as sarcoidosis or infectious diseases such as tuberculosis, syphilis, and fungal infections or proliferative disorders such as Langerhans cell histiocytosis, Erdheim–Chester disease and neoplastic conditions such as germinoma, craniopharyngioma and lymphoma can cause hypophysitis.

Anti-PIT1 hypophysitis is a recently identified form characterized by circulating PIT1 autoantibodies, though cytotoxic T lymphocytes are responsible for the disease [2]. PIT1 is a transcription factor involved in the differentiation of thyrotroph, somatotroph and lactotroph cells during organogenesis. Clinically, it is characterized by the selective deficiency of GH, TSH and prolactin. Anti-PIT1 hypophysitis is a paraneoplastic condition, with thymoma as the most common underlying tumor [2]. Finally, acquired isolated ACTH deficiency is a novel paraneoplastic form of pituitary autoimmunity discovered in a patient with an ectopic ACTH-expressing neuroendocrine carcinoma who subsequently developed ACTH deficiency [2]. Serum anti-proopiomelanocortin (POMC) antibodies and peripheral POMC autoreactive blood lymphocytes were found. Isolated ACTH deficiency has also been shown in patients with gastric cancer and leukemia as well as in patients with lymphocytic infiltration of the pituitary gland.

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Autoimmune Parathyroid Disease

54

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Abstract

Chronic hypoparathyroidism (CHP) clinically presents with hypocalcemia associated with its specific signs and symptoms. CHP usually develops following surgical removal of all four parathyroids, while other causes of parathyroid damage are rarer. Autoimmune damage to parathyroids leading to CHP can occur as a part of autoimmune polyendocrine syndromes (APS) or can present as an isolated disease. Autoimmune CHP is marked by the presence of specific autoantibodies and genetic markers which are reviewed here. We also describe a diagnostic algorithm for identifying the autoimmune forms of CHP.

Keywords

Hypoparathyroidism · Autoimmune polyendocrine syndromes · Multiple autoimmune syndromes · AIRE gene · Interferons autoantibodies · NACHT leucine-rich-repeat protein 5 autoantibodies · Calcium-sensing receptor autoantibodies · Autoantibodies against PTH type 1 receptor

Introduction

Chronic hypoparathyroidism (CHP) is a rare endocrine disorder in which the production of parathyroid hormone (PTH) by the parathyroid glands is absent or inappropriately low. The prevalence in the United States and Europe is estimated at 23–37 per 100,000 individuals. The most common cause of CHP is damage or removal of the parathyroid glands during neck surgery, accounting for approximately 75% of all the cases. Other causes of CHP can be due to autoimmune damage, genetic disorders or infiltrative diseases [1, 2]. In this review, we evaluate the history, diagnosis, clinical manifestations, genetic, autoantibody markers, and therapy of the autoimmune forms of CHP.

History

As reviewed previously [3], "idiopathic" CHP was first described in 1928, and in 1929, the first case of CHP associated with moniliasis was reported. In 1943, five cases of CHP were reported (three of whom were siblings), and one of them was associated with both chronic mucocutaneous candidiasis (CMC) and Addison's disease (AD). In 1957, the following criteria were proposed for defining a disease as autoimmune: (a) induction of the disease in animals by immunization with autoantigens and passive disease transfer by serum or lymphocytes; (b) demonstration of circulating autoantibodies; (c) demonstration of lymphocytic and plasma cells infiltration in the target organs. When 75 cases of CHP described in the literature were reviewed in 1962, in 11 cases of CHP associated with AD, the autopsy evaluation revealed the pathology of the parathyroids characterized by gland atrophy with mononuclear cell infiltration and in some cases a complete atrophy of the parathyroids. In addition, the histopathology of adrenals also showed pronounced atrophy, lymphocytic infiltration and fibrosis, indicating a common pathological background for both diseases. In 1966, parathyroid autoantibodies were demonstrated for the first time by

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the indirect immunofluorescence technique (IIF). Based on these observations and according to the criteria for autoimmune diseases, CHP that was previously described as idiopathic, had been recognized as an autoimmune disease. However, the history regarding the presence of autoantibodies directed against parathyroid cells in patients with CHP is rather complicated and is described in more detail in a separate section herein (see the paragraph on autoantibodies).

Classification of Autoimmune CHP

Autoimmune Polyendocrine Syndrome type 1 (APS-1), also called Autoimmune-Poly-Endocrine-Candidiasis-Ectodermal-Dystrophy (APECED), is a rare disease presenting at a young age, characterized by the presence of a triad of main diseases where CHP is in general preceded by CMC and followed by autoimmune AD (AAD). A review of 989 cases of patients with APS-1 described worldwide showed that CHP tended to develop at a mean age of 6 years (range 4–10 years), was preceded by CMC at a mean age of 4 years (range 1–8 years) and followed by AAD at a mean age of 9 years (range 6–13 years) [4]. In addition, during a lifetime, the patients with APS-1 can develop other autoimmune diseases (such as premature ovarian insufficiency (POI), autoimmune gastritis/pernicious anemia, autoimmune intestinal disease, autoimmune hepatitis, type 1 diabetes mellitus, autoimmune thyroid diseases, alopecia, vitiligo, pituitary dysfunctions, spleen atrophy) and non-autoimmune diseases (such as nail dystrophy, keratoconjunctivitis, cataract, calcification of the basal ganglia, cholelithiasis, enamel hypoplasia, periodic fever with rash, non-infectious keratitis) [5, 6]. APS-1 is an autosomal recessive syndrome caused by mutations of the autoimmune regulator (*AIRE*) gene located on chromosome 21 (21q22). This syndrome is marked by the presence of interferons autoantibodies (IFNsAbs) [7] and, in patients presenting with CHP, also by autoantibodies against NACHT leucine-rich-repeat protein 5 (NALP-5Abs) [2, 6, 8]. It is still debated whether antibodies to calcium-sensing receptor (Ca^+SRAbs) can be considered as markers of autoimmune CHP (see the paragraph on autoantibodies).

Historically, the diagnosis of APS-1 was based on the presence of at least two of the three main diseases [9]. In 2018, new diagnostic criteria recommended addition of testing for IFNsAbs in patients presenting with one of the following diseases before the age of 30 years: CMC, AD, CHP, POI, enamel hypoplasia, periodic fever with rash, non-infectious keratitis and autoimmune hepatitis. If testing for IFNsAbs is not available, it is recommended to proceed directly with *AIRE* gene analysis [7]. Outside of APS-1, CHP can be associated either with clinical, subclinical or potential autoimmune thyroid diseases (AITD), such as Hashimoto's thyroiditis or Graves' disease and in these cases becomes a component of APS-3 [5, 10]. CHP can also be associated with other clinical, subclinical or potential autoimmune diseases not included in APS-1 or APS-3 (for example autoimmune gastritis, pernicious anemia, celiac disease, vitiligo, alopecia, myasthenia gravis, rheumatoid arthritis, Sjogren's syndrome, SLE, etc.) and classified as APS-4 [5, 10]. In the absence of associated specific clinical, subclinical or potential autoimmune diseases, only the presence of AIRE gene mutations [6] or of class I HLA A*2601, Class II HLA DRB1*010 or DRB1*09 would suggest an autoimmune background of seemingly isolated CHP [2, 11, 12].

In addition to autoimmunity, CHP can be due to vascular damage, neck irradiation, infiltrative diseases or rare genetic disorders characterized by impaired PTH production or secretion, or to a defective gland development. Mutations of genes encoding for PTH, glial cells missing 2 (GCM2) or Ca^+SR have been described, particularly in patients with familial isolated CHP; however, these mutations are very rare in non-familial cases [1, 2]. All other cases of CHP are considered idiopathic.

Epidemiology

The data on the global prevalence of non-surgical CHP are limited. An estimated prevalence of idiopathic CHP of 1.2 cases per million population was reported from Israel [3] while a period prevalence of 7.2 cases per million with an annual incidence rate of 0.72 cases per million population was described in Japan [3]. In contrast, more data are available on the worldwide prevalence of APS-1 where CHP is one the fundamental diseases. The highest prevalence was detected in the Iranian Jewish population (1 case per 9000 individuals), followed by Finland (1 per 25,000 individuals), Norway (1 per 90,000 individuals), Poland (1 per 129,000 individuals), Ireland (1 per 130,000 individuals), France (1 per 500,000 individuals) and Japan (1 per 10 million individuals) [6]. In Italy, the prevalence of APS-1 was 2.6 cases per million, with some "hot spot" areas in Sardinia (17 cases per million) or in Veneto (5 cases per million) [6]. Among APS-1 cases worldwide at the end of a long follow up a majority (50–100%) of patients eventually presented with CHP [6]. CHP association with AITD (APS-3) is observed in 18% of reported cases [10] while the association of CHP with other autoimmune diseases (APS-4) is rarely present [5].

Genetic

APS-1 is caused by autosomal recessive mutations of *AIRE* gene on chromosome 21 (21q22.3). *AIRE* gene plays an essential role in the central tolerance. Mutations in the *AIRE* gene prevent the elimination of self-reactive T cells at central level and induce a Treg defect at peripheral levels. This leads to the development of multiple autoimmune diseases at a young age [7]. The most frequent mutation is R257X in exon 6 detectable in 87% of Finnish patients although it was also found in other populations. Mutations C322fsX372 or del13 in exon 8 are typical of Anglo-Saxon populations but can also occur in patients in different populations. To date, more than 126 *AIRE* gene mutations have been identified [6]. The close correlation between AIRE gene mutations and APS-1 was demonstrated in a study of 24 patients with CHP without other autoimmune diseases of whom three patients (12.5%) had both homozygous AIRE gene mutations and the presence of IFNsAbs [13]. CHP presentation in the context of APS-3 or APS-4 can be associated with class I or class II (HLA) alleles but not with AIRE gene mutations [2]. Isolated CHP can be suspected to have autoimmune pathogenesis in the case of a family history of other autoimmune diseases or if associated with class I HLA A*2601, or class II HLA DRB1*010 or DRB1*09 alleles [11, 12].

Autoantibodies

Autoantibodies against parathyroids (PTAbs) were first identified in 1966 using the IIF test in 38% of patients with CHP, in 26% of patients with AAD and in 6% of healthy controls. Further studies in 1969 detected PTAbs by IIF in 11% of patients with CHP, but also in 11% of controls as previously reviewed [3], These confusing results were clarified in 1985 when it was demonstrated that PTAbs did not react against parathyroid chief cells, but against oxyphil cells specifically recognizing a 46 kDa mitochondrial antigen [14]. However, PTAbs reacting against the surface of parathyroid cells capable of mediating a complement-dependent cytotoxicity in cultured parathyroid cells were described in 1986. The specificity of these antibodies was also revised in 1988 when it was shown that they seemed to react with parathyroid endothelial cells as reviewed in more detail previously [3]. In 2006, advancements in diagnosing of APS-1 showed that IFNsAbs, namely omega and alpha subtypes, were present in almost all the patients. Consequently, IFNsAbs could be particularly helpful in early diagnosis of APS-1 being present also in patients with only a single component disease of APS-1 [2, 7]. Therefore, IFNsAbs positivity in patients with CHP have an important diagnostic value for APS-1. In addition, NALP-5Abs were reported for the first time in 2008 in 49% of patients with CHP in the context of APS-1 of whom many had a long-standing disease at the time of antibody measurements [8]. NALP-5Abs and IFNsAbs are specific markers for CHP in the context of APS-1 and are absent in patients with isolated CHP or in the context of APS-3 or APS-4. NALP-5Abs are negative in patients with other autoimmune diseases and in healthy controls [8]. The absolute association of NALP-5Abs with CHP in APS-1 was confirmed in a study on 145 patients with isolated CHP, where the only patient positive for NALP-5Abs was also positive for AIRE gene mutations, confirming the diagnosis of APS-1 [3, 15]. Calcium-sensing receptors (Ca^{+}SR) are highly expressed on parathyroid chief cells. These receptors are sensitive to the serum concentrations of calcium and modulate the synthesis and production of PTH [2]. The high levels of expression of the Ca^{+}SR on PTH-producing cells had led to it being investigated as a candidate parathyroid autoantigen in patients with CHP. The presence of Ca^{+}SRAbs was demonstrated for the first time in 1996 [16] in 25 patients with CHP of whom the majority had APS-1. The Ca^{+}SRAbs positivity greatly varied depending on the methodology with 56% detected using immunoprecipitation assay (IPA), 32% with Western blot (WB) analysis using human embryonal kidney (HEK)-293 cells expressing the Ca^{+}SR or 20% with WB using human parathyroid extracts. None of the healthy controls were positive [3]. Subsequent studies identified Ca^{+}SRAbs positivity in a very wide range from 0% to 90% of patients using different assays, different lengths of the Ca^{+}SR molecule (full-length or the extra-cellular domain) and different patients (with isolated CHP or with CHP and APS-1). Furthermore, the range of positivity varied from 0% to 22.5% in controls [2, 3]. Finally, some authors demonstrated that Ca^{+}SRAbs may display the activating or inhibiting activity for the Ca^{+}SR and thus could be considered pathogenetic markers for CHP [17]. Given such variable results, it would be appropriate for an International Standardization Program to be undertaken to establish whether Ca^{+}SRAbs are indeed true markers of autoimmune CHP and what is the best detection method. Recently a new form of autoimmune parathyroid hormone (PTH) resistance due to IgG autoantibodies against PTH type 1 receptor (PTH1RAbs) capable of blocking the PTH and inducing hypocalcemia with increasing levels of PTH was described in two exceptional patients with other autoimmune diseases [18]. The various forms of autoimmune CHP identified to date are summarized in Table 54.1.

Table 54.1 Classification of autoimmune CHP

Age	CHP	Genetic markers	Autoantibody markers	Syndromes or disease
<30 years	Isolated or associated with CMC, AAD, or with other autoimmune or non-autoimmune diseases typical of APS-1	Presence of AIRE Gene mutations	Presence of IFNsAbs, and/or NALP-5Abs, Ca^{+}SRAbs (?)	**APS-1**
Adult	Associated with clinical, subclinical or potential AITD (Hashimoto's thyroiditis or Graves' disease)	Negative for AIRE Gene mutations	Presence of TPOAbs and/or TgAbs and/or TRAbs	**APS-3**
Adult	Associated with other clinical, subclinical or potential autoimmune diseases (except for AITD)	Negative for AIRE Gene mutations	Presence of other organ or non-organ specific Abs	**APS-4**
Adult	Without other clinical, subclinical or potential autoimmune diseases	Presence of HLA A*2601, DRB1*010, DRB1*09	Negative for IFNsAbs and for other Abs	**Isolated autoimmune CHP**
Adult	With other autoimmune disease	Unknown	Presence of PTH1RAbs	**Autoimmune CHP**
Adult	Without any other clinical, subclinical or potential autoimmune diseases	Negative for AIRE gene mutations and for HLA A*2601, DRB1*010, DRB1*09	Negative for IFNsAbs and for other Abs	**Idiopathic CHP**

AAD autoimmune Addison's disease, *AIRE* AutoImmune REgulator, *AITD* auto-immune thyroid diseases, *APS* autoimmune polyendocrine syndrome, *Ca+SRAbs* calcium-sensing receptor autoantibodies, *CHP* chronic hypoparathyroidism, *CMC* chronic mucocutaneous candidiasis, *HLA* human leucocyte antigen, *IFNsAbs* interferons autoantibodies, *NALP-5Abs* NACHT leucine-rich-repeat protein 5 Autoantibodies, *PTH1RAbs* autoantibodies against PTH type 1 receptor, *TgAbs* thyroglobulin autoantibodies, *TPOAbs* thyroperoxidase autoantibodies, *TRAbs* TSH-receptor autoantibodies, *Abs* autoantibodies

Animal Models and Cell-Mediated Immunity

As reviewed previously [3], an animal model of parathyroiditis induced by injection of parathyroid homogenate was demonstrated in 1965 and a spontaneous animal model of APS with CHP was described in 1991. In patients with CHP, a lymphocytic infiltration of the parathyroid was first demonstrated in 1962 and subsequently confirmed in 1971 and 1973 [2, 3]. Furthermore, the evidence of cell-mediated immunity in CHP patients manifested by an increased number of circulating activated T-cells, including Ca^{+}SR reactive T-cells compared to control were also shown [2].

Physiology

PTH is synthetized and secreted by parathyroid chief cells and plays a fundamental role in mineral homeostasis by promoting renal reabsorption of calcium and stimulating renal phosphate excretion. It also promotes conversion of 25-hydroxyvitamin D to its active form 1,25-dihydroxyvitamin D which increases the absorption of calcium and phosphate from the gastrointestinal tract. Moreover, PTH is a regulator of bone turnover [1]. The diagnostic findings in patients with autoimmune CHP include hypocalcaemia, hyperphosphatemia, hypercalciuria, reduced levels of 1,25-dihydroxyvitamin D, low levels of PTH and overly mineralized bone [1]. However, it should be noted that the levels of total calcemia are influenced by the serum levels of albumin. One formula used for calculating the adjusted calcium concentration is as follows: adjusted calcium (mg/dL) = total calcium (mg/dL) + [(4.0 − albumin (g/dL) × 0.8] [2]. Alternatively, ionized calcium may be determined. Hypomagnesemia may also give rise to hypocalcemia, by inducing either a resistance to PTH or a diminished secretion of PTH. In patients with hypomagnesemia, hypocalcemia is difficult to correct without first normalizing the serum magnesium concentration.

Diagnosis and Clinical Manifestations

The diagnosis of CHP is based on the low serum levels of albumin-adjusted total calcium or of ionized calcium in the presence of undetectable or inappropriately low levels of endogenous PTH in a patient without hypomagnesemia. Hypomagnesaemia may be one of the reversible causes of hypoparathyroidism while other potentially reversible causes include iron or copper overload. CHP typically manifests as perioral numbness, paresthesia, neurocognitive deficits, weakness, carpo-pedal muscle spasms, cardiac arrhythmias, laryngeal spasm and tetany. Focal or generalized seizures can also occur [1]. Latent hypocalcemia can be revealed by Chvostek's and Trousseau's signs, which are hallmarks of neuromuscular irritability. Cardiovascular manifestations are common, varying from electrocardiographic abnormalities to chest pain with increased markers of cardiac muscle injury and heart failure. Hypocalcaemia characteristically induces a prolongation of the QT interval in the electrocardiogram, and this may trigger dysrhythmias such as polymorphic ventricular tachycardia (*torsades de pointes*). Neuropsychological dysfunctions like anxiety, depression, emotional instability and, less commonly, mental confusion, hallucination and overt psychosis have recently been demonstrated [1]. All these symptoms are reversible with treatment normalizing calcium levels. Basal ganglia calcifications (Fahr's syndrome) are another frequent marker of CHP present from 12% to 74% of the patients with CHP and are associated with neurological symptoms including extrapyramidal and cerebellar disorders, cognitive and psychiatric impairment, and epilepsy [19]. These calcifications are not reversible, and symptoms do not revert with normalization of serum calcium levels because the damage to neurological structures has already occurred.

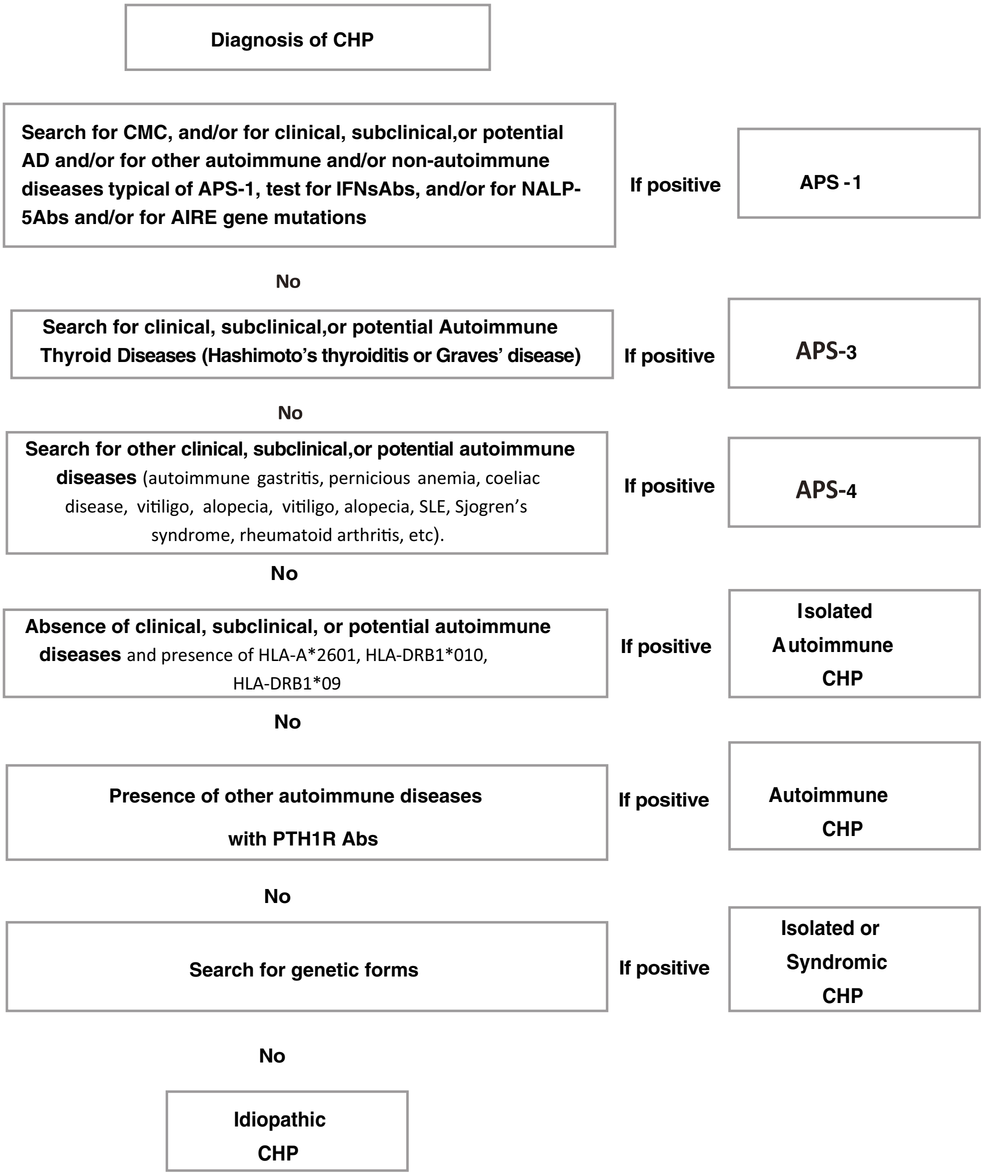
Therapy

Severe symptoms of hypocalcemia, like seizures or laryngospasm, require prompt treatment with intravenous infusion of calcium gluconate until reversal of symptoms and normalization of calcium levels. Long-standing therapy of CHP is based on oral calcium and the active form of vitamin D 1,25-dihydroxyvitamin D. In CHP, active vitamin D formation is impaired in the kidney because of the lack of PTH. Calcitriol is the vitamin D metabolite of choice because of its faster action and shorter half-life compared to other preparations, thus making it more suitable for chronic treatment. Cholecalciferol should also be added because of its potential pleiotropic effects at the systemic level. A diet rich in calcium is the best strategy to reduce or avoid the supplementation with oral calcium carbonate or citrate. The clinical target is to control symptoms of hypocalcemia, maintaining the total serum calcium at the lower levels of the normal range and avoiding hypercalciuria. The efficacy, safety and adverse effects of treatment with recombinant PTH have been assessed in a systematic review and meta-analysis of currently available randomized controlled trials and conventional therapy in the management of patients with CHP [20]. Seven randomized trials reported in 12 publications enrolled a total of 386 patients with the follow-up ranging from 1 to 36 months. Many studies have shown that hypocalcemia can be adequately controlled by means of once- or twice-daily subcutaneous injection of teriparatide (PTH 1-34) or intact PTH (PTH 1-84). The overall results of the meta-analysis suggest a small impact of PTH therapy on physical health-related quality of life. However, the benefits include a reduction in serum phosphate. The reduction in phosphate may have important benefits of lowering the long-term complications of CHP and requires further studies. Furthermore, treatment with PTH allowed to reduce the dose of the calcium and active vitamin D in some patients. The adverse events with PTH therapy may be related to a higher incidence of hypercalcemia in comparison to conventional treatment. There was no other convincing evidence of adverse events [20]. These observations may support the use of PTH therapy in patients with CHP. However, due to the limitations of short duration of therapy and small sample size, evidence from randomized trials regarding benefits of PTH therapy compared with conventional therapy remains incomplete and will require further studies.

Conclusions

CHP may be a diagnostic challenge from a clinical point of view, and establishing its etiology may be difficult. The parathyroid glands are an uncommon target for autoimmunity and, except for CHP in the context of APS-1, APS-3 and APS-4, the isolated form of CHP today remains a putative autoimmune disease. Once the CHP diagnosis is confirmed, further investigations should include: (a) family history of autoimmune diseases, (b) patient history of other clinical, subclinical or potential autoimmune diseases, (c) AIRE gene mutations, class I or II HLA, (d) IFNsAbs and NALP-5Abs. An algorithm for the diagnosis of CHP is shown in Fig. 54.1. Early diagnosis, optimal treatment and close monitoring are essential in the long-term management of CHP patients.

Fig. 54.1 Algorithm for the diagnosis of autoimmune chronic hypoparathyroidism (CHP)


Diagnosis of CHP
Search for CMC, and/or for clinical, subclinical,or potential AD and/or for other autoimmune and/or non-autoimmune diseases typical of APS-1, test for IFNsAbs, and/or for NALP-5Abs and/or for AIRE gene mutations
If positive
APS -1
No
Search for clinical, subclinical,or potential Autoimmune Thyroid Diseases (Hashimoto's thyroiditis or Graves' disease)
If positive
APS-3
No
Search for other clinical, subclinical,or potential autoimmune diseases (autoimmune gastritis, pernicious anemia, coeliac disease, vitiligo, alopecia, vitiligo, alopecia, SLE, Sjogren's syndrome, rheumatoid arthritis, etc).
If positive
APS-4
No
Absence of clinical, subclinical, or potential autoimmune diseases and presence of HLA-A*2601, HLA-DRB1*010, HLA-DRB1*09
If positive
Isolated Autoimmune CHP
No
Presence of other autoimmune diseases with PTH1R Abs
If positive
Autoimmune CHP
No
Search for genetic forms
If positive
Isolated or Syndromic CHP
No
Idiopathic CHP

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Autoimmune Polyendocrine Syndromes

55

Maurizio Cutolo and Emanuele Gotelli

Abstract

Autoimmune polyendocrine syndromes (APSs) are defined as multiple autoimmune-mediated endocrine gland failures. The current classification criteria of APSs propose four main presentations, based on clinical features.

APS-1 is characterized by three main clinical conditions: chronic mucocutaneous candidiasis, chronic hypoparathyroidism and Addison's disease (AD). APS-2 (or Schmidt syndrome) is a combination of AD, autoimmune thyroid disease (TAD) and/or type 1 diabetes. APS-3 is defined as an association between TAD and another systemic or organ-specific autoimmune disease. Because TAD is the most prevalent autoimmune condition in the general population, APS-3 is the most frequently observed autoimmune polyendocrine syndrome. APS-4 includes other combinations of the autoimmune disorders previously described, which cannot be allocated in other APS definitions.

Most of the autoimmune endocrine diseases of APSs are characterized and preceded by the development of organ-specific autoantibodies, usually directed to antigens expressed by endocrine cells. Different authors have suggested a common pathogenesis, basing on a similar mononuclear leukocyte infiltration and the detection of organ-specific autoantibodies.

Keywords

Autoimmune polyendocrine syndromes · Addison disease · Diabetes mellitus · Thyroid autoimmune disease · Chronic mucocutaneous candidiasis · Chronic hypoparathyroidism · Autoantibodies · AIRE gene

The concept of "shared autoimmunity" is widely used to define clinical situations in which several complete or incomplete features of autoimmune diseases are simultaneously detected in the same patient, because of genetic or environmental factors. This is the case of "autoimmune polyendocrine syndromes" (APSs) or "autoimmune polyglandular syndromes" that are classically defined as a multiple autoimmune-mediated endocrine gland failure [1].

The first case report was described in 1855 as a combination of pernicious anemia, vitiligo and idiopathic adrenal insufficiency. Different authors have suggested a common pathogenesis of the different types of APSs, basing on a similar mononuclear leukocyte infiltration observed in some goitrous thyroid glands, in adrenal cortex of Addison's patients and in pancreatic islets of subjects with type 1 diabetes (T1D) [1]. During the 1950s, other authors suggested a second pathogenetic mechanism, assuming an endocrine dysfunction, due to the detection of organ-specific autoantibodies, such as anti-thyroid antibodies in patients with Hashimoto's thyroiditis. The nature of the relationship between anti-thyroid autoimmunity and the pathogenesis of autoimmune diseases is currently unknown. Some authors have demonstrated that anti-thyroglobulin antibodies can form immune complexes, and anti-microsomal antibodies not only bind to thyroid peroxidase but also modulate natural killer cell activity in autoimmune thyroiditis [2]. An alteration of the immune regulation and the occurrence of circulating autoantibodies, directed against antigens expressed by endocrine cells, are nowadays the two major pathogenetic hypotheses explaining the glandular failures in different APSs.

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Table 55.1 Classification of different autoimmune polyendocrine syndromes (APS) [3]

Disease associations	
APS-1	Chronic mucocutaneous candidiasis, chronic hypoparathyroidism, Addison's disease (two of three present)
APS-2	Addison's disease (always present) with autoimmune thyroid diseases and/or type 1 diabetes
APS-3A	Autoimmune thyroid diseases and type 1 diabetes
APS-3B	Autoimmune thyroid diseases and atrophic gastritis/pernicious anemia
APS-3C	Autoimmune thyroid diseases and any organ-specific autoimmune disease (excluding Addison's disease)
APS-4	Any combination of two or more autoimmune diseases that are not included in APS-1, APS-2, APS-3A, APS-3B, APS-3C

Then, Neufeld and Blizzard suggested a systematic classification of APSs in 1980, based on clinical criteria only, describing four main presentations (Table 55.1) [3].

APS-1

Originally described in 1929, APS-1 is a very rare syndrome (prevalence from 1:9000 to 1:200,000 in general population), characterized by three main clinical features: chronic mucocutaneous candidiasis, chronic hypoparathyroidism and Addison's disease (AD) [1]. For this reason, APS-1 is also termed autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED). Although two of the three major criteria are sufficient for the diagnosis, most patients have all the major clinical components of the syndrome [1].

Pathogenesis

APS-1 is an autosomal recessive syndrome mainly caused by different mutations of a regulatory gene, called "AIRE" (Autoimmune Regulator), located on chromosome 21 [4]. More than 100 different mutations have been identified as missense mutations, insertions and deletions leading to the alteration of functional properties of intracellular proteins. Although a single mutation of AIRE gene can be directly responsible for APS-1, the clinical expression of the syndrome depends on the same mutation on both AIRE alleles [1]. AIRE is expressed in medullary thymic epithelial cells and encodes for the transcription of tissue-specific antigens. Moreover, AIRE induces the expression of FoxP3$^+$ regulatory T cells (Tregs), which have the task of eliminating autoreactive T cells [5, 6]. AIRE mutations lead to altered immunological tolerance and abnormal negative selection of self-reactive T cells [6]. When self-antigens are not expressed by thymocytes and FoxP3$^+$ T regs are absent, autoreactive T cells can cause autoimmune systemic damage to different organs.

As a consequence, several auto-antibodies are identifiable in the peripheral circulation of APS-1 patients. In patients with hypoparathyroidism there are autoantibodies against anti-calcium-sensing-receptors and NALP5 (NACHT, leucine-rich repeat, pyrin domain-containing protein 5), both expressed by parathyroid glands [7, 8].

In AD, a variety of autoantibodies against adrenal cortex intracellular enzymes have been reported, especially directed against the antigen 21-hydroxylase (21-OH), side-chain cleavage (SCC) enzyme and 17a-hydroxylase [5]. Almost all APS-1 patients with AD show autoantibodies against at least one of these proteins, but only 21-OH and SCC enzyme are considered major antigens and the most specific autoantibody targets.

Other autoantibodies are described as markers of minor autoimmune features in APS-1. Antibodies against tryptophan hydroxylase can be associated with autoimmune enteritis in APS-1 [5]. Anti-GAD65 (glutamic acid decarboxylase 65) and anti-IA2 (tyrosine phosphatase-like protein IA2) seem to predict the development of T1D in APS-1. In addition, auto-antibodies against pituitary protein 6 have been detected in patients with GH deficiency [9].

Auto-antibodies against melanin-producing cells, anti-aromatic amino acid decarboxylase and anti-transcription factors Sox9 and Sox10 are associated with vitiligo in APS-1 [10]. Sox10 is involved in the differentiation of tissues derived from the neural crest and in the migration of melanoblasts to dermis during differentiation. A specific reactivity of auto-antibodies against Sox10 has been found in about 63% of patients with APS-1 and vitiligo, while all auto-antibodies against Sox10 display a reactivity also against Sox9 [10].

Finally, auto-antibodies directed against interferons are present in almost all patients with APS-1, even if they have not been associated to a specific disease domain [11].

Clinical Features

A chronic Candida infection can represent the first clinical presentation of APS-1, generally occurring during the first years of life. It involves nails, skin and mucous membranes (oral mucosa, esophagus), and it is probably due to a selective T-lymphocyte defect against *Candida albicans*. In contrast, these patients maintain a normal B-cell response, which prevents the development of a systemic candidiasis [1].

Chronic hypoparathyroidism, usually onset before age 15, can be clinically recognized by paresthesia, neuromuscular hyperexcitability (sometimes with tetany), hypotension and malabsorption (with steatorrhea), and is always associated with hypocalcemia and hyperphosphatemia.

AD can onset between months 6 to age 40, with clinical manifestations of a combined deficiency of mineralocorticoids, glucocorticoids and sex hormones (estrogens and androgens). Non-specific symptoms, such as generalized weakness, fatigue, weight loss and anorexia, are usually reported by patients. However, a full-blown adrenal failure could lead to gastrointestinal involvement (nausea, vomiting, abdominal pain), cardiovascular symptoms (hypotension or syncope), hypoglycemia and sexual hormones-related dysfunctions, such as secondary amenorrhea (detectable in 25% of female patients) and hypergonadotropic hypogonadism (25–60% of cases), with testicular/primary ovarian insufficiency [1].

Other clinical features are reported in patients affected by APS-1, and they are defined as minor clinical manifestations. Skin involvement is characterized by alopecia areata, localized at scalp or spread to axillary and pubic hair (universal alopecia), vitiligo, nail and teeth dystrophy (enamel hypoplasia). Ocular involvement (keratitis, retinitis), autoimmune enteritis with malabsorption and autoimmune liver diseases are reported in a minority of cases [1], while T1D, atrophic gastritis or vitiligo are more rarely described [1]. Table 55.2 shows the frequency of major and minor clinical features of APS-1.

Diagnosis

A diagnosis of APS-1 can be suspected, when chronic mucocutaneous candidiasis, hypoparathyroidism and AD are present. The clinical diagnosis of mucocutaneous candidiasis can be confirmed by a microscopic examination of a swab of the lesions which can reveal fungal hyphae, as well as by coltures on specific media. Esophagogastroduodenoscopy or colonoscopy are performed only in selected cases to evaluate the rare occurrence of Candida systemic infection.

Chronic hypoparathyroidism is always characterized by hypocalcemia, hyperphosphatemia and low urinary levels of calcium, with increased urinary phosphorus. Parathyroid hormone serum concentrations are low or undetectable. Autoantibodies against anti-calcium-sensing-receptors and NALP5 are not routinely searched.

A full-blown AD shows hyponatremia, hypochloremia, hyperkalemia and a mild persistent eosinophilia. The correct assessment of adrenocorticotropic hormone (ACTH) and cortisol serum concentrations must be performed early in the morning: ACTH is usually increased, while cortisol is reduced. Aldosterone and dehydroepiandrosterone are frequently reduced in the serum. Autoantibodies against 21-OH are usually found in AD.

To confirm the clinical suspicion of APS-1, in the presence of two major clinical features, sequencing of AIRE gene is indicated, which can reveal mutations in 92% of patients [4]. However, when only one major clinical feature of APS-1 is present in association with some of the minor clinical features, these patients should be screened first for anti-interferon autoantibodies [5]. In case of positivity, it is also indicated to proceed in these cases with the sequencing of the AIRE gene.

Table 55.2 Major and minor clinical features of APS-1 [4]

	Percentage (%)
Major clinical features of APS-1	
Chronic mucocutaneous candidiasis	100
Chronic hypoparathyroidism	79
Addison's disease	72
Minor clinical features of APS-1	
Enamel hypoplasia	77
Alopecia areata	29
Vitiligo	13
Keratitis/retinitis	35
Autoimmune enteritis	18
Atrophic gastritis	13
Type 1 diabetes	12

APS-2

APS-2 (or Schmidt's syndrome) is characterized by a combination of AD, autoimmune thyroid diseases (TAD) and/or T1D [1] (Table 55.3). It usually affects adults, with a predominant female prevalence (3:1) and the average age of disease onset is 35 years [1, 12].

Pathogenesis

APS-2 is a polygenic disease and several allelic variations of the genes coding for the major histocompatibility complex (MHC) have been involved in the pathogenesis [1]. An increased prevalence of HLA-DR3 or DR4 aplotypes has been found, especially in patients with T1D (DR4, DQB10302) [1].

Table 55.3 Major and minor clinical features of APS-2 [12]

	Percentage (%)
Major clinical features of APS-2	
Addison's disease	100
Thyroid autoimmune diseases	70–82
Type 1 diabetes	30–50
Minor clinical features of APS-2	
Vitiligo	4.5–11
Atrophic gastritis	4.5–11
Vitiligo	13
Hypogonadism	4.5–9
Autoimmune hepatitis	4
Alopecia	1–4

The aplotype DR3/DR4 is a risk factor (relative risk of 2.7–3.2) for the development of APS-2, while the presence of other alleles (DR1, DR7, DR13 and DR14) seems to be protective [11]. A higher frequency of HLA DQA1 (0301) aplotype seems to be strictly associated with APS-2, with no specific association with any of its clinical features, except for alopecia. Of note, variants in DR3-DQ2 and DR4-DQ8 aplotypes are clearly associated with celiac disease, but at the same time also with AD, T1D and TAD [5]. Recently, other mutations predisposing to APS-2 have been identified in non-HLA genes, encoding CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4), PTPN22 (protein tyrosine phosphatase, nonreceptor type 22) and CD25-interleukin-2 receptor [13–15].

Clinical Features

All the patients show a classical AD, associated to TAD in 70–82% of cases [1]. Most of them develop Graves' disease, generally before AD, or Hashimoto's disease, that can occur before or after the diagnosis of AD. T1D can be present in about 30–50% of patients. Moreover, different authors have reported an incomplete APS-2, characterized by only one constitutive disease of the syndrome with only serum autoantibodies for other APS-2 components [11]. Minor clinical manifestations of APS-2 are also shown in Table 55.3.

Diagnosis

Diagnostic investigations for AD are the same previously described.

Autoimmune thyroid diseases are characterized by specific anti-thyroid antibodies, namely anti-thyroglobulin and anti-thyroid peroxidase antibodies, which can be tested by most routine laboratories. Non-organ specific autoantibodies, such as antinuclear antibodies (ANAs), can be detected in about one-third of patients affected by TAD.

In contrast, autoantibodies associated to T1D (anti-islet-cell, anti-GAD65 and anti-IA2) in APS-2 are not usually tested [1].

APS-3

APS-3 is defined as an association between TAD and another systemic or organ-specific autoimmune disease, except for AD (Table 55.1) [1]. Because TAD is the most prevalent autoimmune condition in the general population, APS-3 is the most frequently observed autoimmune polyendocrine syndrome. Recently, given the wide spectrum of different autoimmune disorders involved, some authors have suggested a new classification of APS-3 (Table 55.4) [16].

Table 55.4 New proposed classification for APS-3, according to Betterle 2023 [16]

APS-3A	APS-3B	APS-3C	APS-3D
Thyroid autoimmune disease (Graves' disease, Hashimoto's thyroiditis) *plus*			
Autoimmune endocrine disease (excluding Addison's disease)	Autoimmune gastrointestinal or hepato-biliary or exocrine pancreas disease	Autoimmune skin or nervous system or hematologic system disease	Autoimmune connective tissue or cardiac disease or systemic vasculitis
Type 1 diabetes	Atrophic gastritis	Vitiligo	Rheumatoid arthritis
Chronic hypoparathyroidism	Pernicious anemia	Alopecia areata	Still's disease
Premature ovarian failure	Celiac disease	Bullous pemphigoid	Cutaneous lupus erythematosus
Autoimmune hypothalamitis	Ulcerative colitis	Pemphigus vulgaris	Systemic lupus erythematosus
Lymphocytic adeno-hypophysitis	Crohn's disease	Dermatitis herpetiformis	Mixed connective tissue disease
Lymphocytic neuro-hypophysitis	Autoimmune hepatitis (type 1 and type 2)	Chronic idiopathic urticaria	Systemic sclerosis
Hirata's syndrome	Primary biliary cholangitis	Myasthenia gravis	Idiopathic inflammatory myopathies
	Primary sclerosing cholangitis	Multiple sclerosis	Sjogren's syndrome
	Autoimmune pancreatitis	Stiff man's syndrome	Anti-phospholipids syndrome
		Lambert–Eaton's syndrome	Rheumatic fever
		Guillain–Barrè syndrome	Idiopathic myocarditis
		Autoimmune hemolytic anemia	Idiopathic heart blocks
		Autoimmune thrombocytopenia	Systemic vasculitis
		Autoimmune leucopenia	

Clinical Features

APS-3 can be classified into four groups of different disorders, according to the main systems involved such as endocrine, gastrointestinal, skin/hematopoietic/nervous system and connective tissue diseases/vasculitis, as shown in Table 55.4 [16]. Analyzing a wide series of patients with TAD, about 52% of the subjects with TAD could show an APS-3, as complete (TAD with another autoimmune disease) or incomplete type (TAD with organ and non-organ specific serum autoantibodies) [11]. Moreover, TAD could be detected in about 10% of the patients affected by T1D, and it is a very common finding also in patients affected by systemic autoimmune diseases, such as systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), Sjogren's syndrome (SS) and rheumatoid arthritis (RA) and further complicates the complex management [17–20].

Diagnosis

TAD can be diagnosed testing thyroid hormones serum concentrations, detecting anti-thyroid autoantibodies (anti-thyroglobulin and anti-thyroid peroxidase) and performing thyroid ultrasound. Non-organ specific autoantibodies, such as antinuclear antibodies (ANAs), can be detected in about one-third of patients affected by TAD, and they represent the hallmark of different systemic autoimmune diseases, taking part of APS-3 [1].

Non-organ specific autoantibodies, such as ANA, anti-ENA and anti-dsDNA antibodies, show a pivotal role in the correct diagnosis of systemic autoimmune diseases, as isolated or associated to TAD in APS-3. ANAs are usually positive in 96–100% of patients affected by SLE, MCTD and Systemic sclerosis (SSc) and in 50–70% of SS, dermatomyositis/polymyositis and RA patients. Some antinuclear specificities can be considered "diagnostic markers" of disease, such as anti-dsDNA and anti-Sm in SLE, anti-Ro/SSA and anti-La/SSB in SS, anti-Scl70 (Topoisomerase I) and anti-centromere in SSc or anti-U1RNP in MCTD. Moreover, in order to define a correct diagnosis of RA, it is mandatory to detect rheumatoid factor and anti-cyclic citrullinated peptide, the marker with high specificity and predictive value for RA.

APS-4

APS-4 includes other combinations of the autoimmune disorders previously described, which cannot be allocated in other APS definitions, for instance AD with hypogonadism, celiac disease or myasthenia gravis [1].

Therapy of APSs

Specific hormone replacement represents the first treatment for adrenal insufficiency and hypothyroidism in APS-1, -2 and -3. Fludrocortisone is indicated for mineralocorticoid deficiency, while hydrocortisone acetate for glucocorticoid deficiency (adjusting the dosage according to patient's acute stress situations, such as infections or surgery) [4]. Levothyroxine is usually used as replacement therapy in hypothyroidism, while methimazole is used to control excessive thyroid hormone release in Graves' disease [4].

Chronic hypoparathyroidism is corrected by the administration of calcium and vitamin D, while insulin therapy for T1D is mandatory.

The chronic mucocutaneous candidiasis of APS-1 is treated with oral mycostatin and oral amphotericin [5]. Oral azole drugs are no longer used in the first line, as they easily develop drug resistance and inhibit steroidogenesis, further worsening the adrenal insufficiency of AD [5].

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Endometriosis

56

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Abstract

Endometriosis is defined as the presence of endometrial-like tissue, glands and stroma, outside the uterine cavity. It is a benign estrogen-dependent chronic inflammatory disease that affects at least 10% of reproductive-age women. Endometriosis is often associated with a range of painful symptoms including chronic pelvic pain and dysmenorrhea. In common with other chronic pain conditions, women with endometriosis often report fatigue and depression. Infertility is significantly more common in patients with endometriosis, with a doubling of risk compared with women without endometriosis. Women with endometriosis also have a high risk of co-occurring or evolving multisite pain and of presenting with other non-malignant gynecologic and non-gynecologic diseases. There is often a long diagnostic delay after onset of symptoms. The availability of robust non-invasive biomarkers for diagnosis, prediction of response to treatment and monitoring of disease progression remain major unmet needs. The diagnosis of endometriosis should be based on patient interview, examination and imaging. As with other chronic inflammatory conditions, treatment should be viewed as a long-term process. The available medical treatments for symptomatic endometriosis work by inhibiting ovulation, lowering serum estradiol levels and suppressing uterine blood flow. The currently available first-line treatments are hormonal, such as progestins and low-dose oral contraceptives. Nowadays, surgery is considered a second-line treatment in most endometriosis patients.

Keywords

Endometriosis · Diagnosis · Comorbidities · Signs and symptoms

Description of the Disease and Classification

Endometriosis is defined as the presence of endometrial-like tissue, glands and stroma, outside the uterine cavity [1]. Nowadays, endometriosis is considered a benign chronic inflammatory disease, which is common in women, and has been underdiagnosed for many years. It frequently affects the ovaries, pelvic peritoneum and uterosacral ligaments. Endometriotic nodules can also be found in the intestinal tract and the urinary system such as the ureter or bladder. The disease may also occur in structures outside the pelvis such as the pleura, pericardium or central nervous system [2]. The disease is estrogen-dependent and affects women in their reproductive years [3]. Today, endometriosis is known to be a systemic disease rather than a disease predominantly affecting the pelvis. The effects of endometriosis extend far beyond the pelvis, causing systemic inflammation, altering liver and adipose metabolism and modifying gene expression at the cerebral level, leading to pain sensitization and mood disorders [1].

Endometriosis is a heterogeneous disease that can be divided into three phenotypes: superficial peritoneal lesions (SUP), ovarian endometriomas (OMA) and deep infiltrating endometriosis (DE). SUP is the least severe form of endometriosis. OMAs are cystic masses that grow inside the ovaries. DE is the most severe form of endometriosis. It is defined as sub peritoneal lesions that penetrate deeper than 5 mm into the tissue or lesions that infiltrate organs such as the bladder, bowel and ureter [3]. As endometriosis is a complex disease with different manifestations, where the relationship between the extent of lesions and symptomatology is not clear, it is difficult to find a definite classification. The four standard classification systems currently used are the rASMR (revised American Society for Reproductive Medicine) classification, the "ENZIAN" classification, the Endometriosis Fertility Index (EFI) and the AAGL (American Association of Gynecological Laparoscopists) classification [1, 2]. Each classification has advantages and disadvantages and the main problem is poor correlation with symptomatology and prognosis and they require a surgical procedure to be fulfilled.

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Epidemiology and Risk Factors

Endometriosis is estimated to affect 10% of reproductive-age women but the true prevalence is still uncertain. Sometimes, women remain asymptomatic and undiagnosed [2]. Endometriosis is often diagnosed late, leading to "unexplained" pain and long-term consequences such as infertility. The average diagnosis delay between onset of symptoms and diagnosis is 10 years, with 65% of women being initially misdiagnosed [2]. The prevalence of endometriosis, including microscopic histological diagnosis, is high (45–50%) in patients with chronic pelvic pain and in asymptomatic women.

There are several predisposing factors associated with the risk of developing endometriosis. The risk factors can be divided into exposure *in utero* and early life such as low birth weight, exposure in childhood and adolescence such as early age at menarche and low body mass index, and exposure in adulthood including short duration of menstrual periods, heavy menstrual bleeding and nulliparity [4], whereas lower risk was consistently associated with higher parity. These factors confirm the hypothesis that endometriosis is closely related to a woman's hormonal environment (estrogen promotes the growth of lesions, and there is progesterone resistance) [2].

Etiopathogenesis

The pathogenesis of endometriosis is complicated and not yet finally clarified. The mechanisms involved are numerous, and their understanding is constantly evolving [5]. Several hypotheses have been proposed, although none of them can fully explain the disease. The main difference between the hypotheses concerns the origin of the endometriotic implants: from inside or outside the endometrium. Therefore, the hypotheses can be divided into two main theories: the *in-situ* theory and the transplantation theory [5–7]. There are six main theories (Table 56.1):

Table 56.1 Theories about the origin endometriosis

– Retrograde menstruation theory
– The coelomic metaplasia theory
– The Mullerian remnant theory
– Endometrial stem cells implantation
– The genetic/epigenetic theory
– The theory of lymphatic and vascular metastasis theory

- Retrograde menstruation theory: this theory states that endometrial-like tissue results from the reflux of eutopic endometrial fragments through the fallopian tubes during menstruation. These cells would subsequently implant and undergo a transition to endometriosis, and then grow onto and into the peritoneum and ovaries. The most important evidence was the demonstration that the reflux of menstrual tissue through the fallopian tubes is a common occurrence in women with open fallopian tubes, detected in 76–90% of women. This is a phenomenon possibly facilitated by dyssynergic uterine contractions. However, this theory cannot explain all cases of endometriosis.
- The coelomic metaplasia theory: this theory states that endometriosis develops from a metaplastic change in the cells of the peritoneum, pleura and ovaries. These metaplastic changes would be triggered by a stimulus, which could be hormonal, infectious or environmental. This theory could explain the occurrence of endometriosis in males, prepubescent and adolescent girls. It may also explain the presence of endometriosis implants in the thoracic cavity.
- The Mullerian remnant theory: this theory mainly explains the presence of endometriosis in the posterior compartment and assumes migration or differentiation of the Mullerian remnants.
- Endometrial stem cells implantation: more recently, endometrial stem progenitor cells were proposed as cells that give rise to the origin of endometriotic lesions, either ectopic or transplanted cells because of their high plastic capacity of differentiation; they may be involved in the etiopathogenesis of benign and malignant endometrial aberrations.
- The genetic/epigenetic theory: this theory affirms that endometriosis originates either from an endometrial cell, a stem cell or a bone marrow cell with genetic or epigenetic defects. After implantation or metaplasia, microscopical and subtle lesions occur; then further genetic or epigenetic alteration, in conjunction with the hormones, immune factors and growth factors in the plasma and peritoneal cavity, leads to typical lesions or cystic ovarian lesions or deep lesions.
- The theory of lymphatic and vascular metastasis theory: this theory suggests that endometrial tissue can circulate through lymphatics and vessels and reach the brain, pleura and retroperitoneal locations.

Endometriosis and Hormonal Regulation

Endometriosis is an estrogen-dependent disease [2]. Ectopic endometrial tissue is dependent on estradiol, an estrogenic steroid hormone, produced both by the ovary and locally by the presence of aromatase in the endometriotic lesion.

There is also increased expression of receptors that bind to estrogens (ER) ER-β and suppression of ER-α in the lesion. ER-α normally induces progesterone receptors (PR); thus, their suppression leads to decreased induction of PR, resulting in progesterone resistance. The main role of progesterone is to inhibit endometrial proliferation, promote decidualization and have an anti-inflammatory effect.

In endometriotic lesions, the ratio of PR-β receptors to PR-α receptors is decreased [2, 6]. This downregulation is caused by epigenetic inhibition of the receptor through an hypermethylation of the promoter.

Endometriosis as an Inflammatory Disease

Endometriosis is nowadays considered an inflammatory disease [1]. Inflammation is another typical feature of endometriosis. The presence of ectopic tissue in the peritoneal cavity is associated with an overproduction of prostaglandins, cytokines and chemokines [6].

Endometriotic implants are sites of local inflammation, which is the cause of pain and infertility associated with this condition [2]. Examination of pelvic fluid of infertile women with endometriosis has revealed higher numbers of peritoneal macrophages.

These macrophages are able to infiltrate the lesions and express factors that promote neoangiogenesis and lesion growth. Macrophages can also accumulate iron, which is probably due to the presence of excessive blood accumulation. Other cytokines or chemokines that are elevated in the peritoneal fluid of patients with endometriosis include macrophage migration inhibitory factor, tumor necrosis factor-α, interleukin (IL)-1β, IL-6, IL-8 and monocyte chemotactic protein-1 among others. Whether the presence of cytokines is the cause or the effect of endometriosis is still unclear [7].

Endometriosis-Associated Symptoms

Endometriosis is often associated with a range of painful symptoms that include chronic pelvic pain (cyclical and non-cyclical), painful periods (dysmenorrhea), painful sex (dyspareunia) and pain on defecation (dyschezia) and urination (dysuria) [1, 2]. Their severity can range from mild to debilitating. Some women have no symptoms, others have episodic pelvic pain, and still others experience constant pain in multiple body regions [8]. In some patients, the cause of the pain appears to be central sensitization and spontaneous activation of trigger points causing myofascial pain. A related observation is that some women transition between these categories, progressing from episodic and localized pain to that which is chronic, complex and more difficult to treat. Furthermore, women with disease that is anatomically "severe" can have minimal symptoms and women with "minimal" evidence of endometriosis can have severe, life affecting symptoms [1, 2]. In common with other chronic pain conditions, women with endometriosis often report experiencing fatigue and depression [2]. Infertility is significantly more common in patients with endometriosis, with a doubling of risk compared with women without endometriosis [9]. Endometriosis is discovered in 30–50% of women who present for assisted reproductive treatment [9].

Endometriosis-Associated or High-Risk Comorbidities

Endometriosis is certainly a multisystem condition, perhaps as a result of common pathogenesis or as a consequence of the chronic endogenous response to the presence of endometriotic lesions [2, 10]. Although pelvic pain is the most common symptom of possible endometriosis, women with endometriosis also have a high risk of co-occurring or evolving multisite pain [8]. Patients with endometriosis have a higher risk of presentation with comorbid chronic pain conditions [2, 11] such as fibromyalgia or migraines (Table 56.2), but also rheumatoid arthritis, psoriatic arthritis and osteoarthritis. Reports of back, bladder or bowel pain (Table 56.2) are prevalent, with dyschezia being potentially predictive of endometriosis [2, 8]. Nearly 50% of women with bladder pain syndrome or interstitial cystitis have endometriosis. Irritable bowel syndrome is another common co-occurring diagnosis that reinforces the importance of awareness of endometriosis among gastroenterologists [8]. These conditions may share a common cause, they may arise together owing to shared environmental or genetic factors, and/or the occurrence of comorbid pain conditions could be due to changes in pain perception after repeated sensitization [8].

Women with endometriosis have a greater risk of presenting with other non-malignant gynecologic diseases, including uterine fibroids and adenomyosis. They are also at greater risk of a subsequent diagnosis of malignancies, early natural menopause and cerebrovascular and cardiovascular conditions [2, 10]. Recent systematic reviews and meta-analyses have found an increased risk of comorbidity of autoimmune disease in endometriosis patients, including systemic lupus

Table 56.2 Pain syndromes associated with endometriosis

– Pain bladder syndrome
– Irritable bowel syndrome
– Vulvar vestibulodynia
– Abdomino-pelvic myalgia
– Viscero-visceral hyperalgesia syndrome
– Central sensitization syndrome
– Tensional headache
– Migraine
– Lumbar pain
– Temporomandibular joint syndrome
– Fibromyalgia
– Chronic fatigue syndrome

erythematosus, Sjögren's syndrome, rheumatoid arthritis or autoimmune thyroid disorders [2, 12]. Indeed, endometriosis seems to have features characteristic of autoimmune diseases, such as an increased presence of autoantibodies [13].

Serologic Features and Biomarkers

The availability of robust non-invasive biomarkers for diagnosis, prediction of response to treatment and monitoring of disease progression remain major unmet needs [2]. Many research studies and Cochrane reviews have assessed potential biomarkers for endometriosis, with the ultimate goal of reducing the delay that exists in diagnosis endometriosis. Unfortunately, all of the candidates investigated to date have proven non-specific or unreliable, making them unappropriated for routine clinical use.

Peripheral levels of Cancer Antigen (CA)-125 have been extensively investigated for the diagnosis of endometriosis [14]. Elevated serum levels of CA-125 are not specific for endometriosis and are also associated with other gynecological and non-gynecological disorders. Although CA-125 is an inexpensive test, its performance in the detection of endometriosis is low. The concomitant dosage of CA-125 and CA-19.9 does not add significant information in respect to the CA-125 test alone in diagnosing endometriosis [14]. Nevertheless, recent studies demonstrate the usefulness of Human epididymis protein (HE)-4 as a key tumor biomarker in patients with OMAs and suspected malignancy showing undetermined risk of malignancy with ultrasonography. In this group of patients, low HE-4 levels suggest a low risk of malignancy [14].

Many autoantibodies have been investigated and found to be elevated in endometriosis patients. Among all the types evaluated, antiendometrial antibodies have been extensively studied and have been suggested as a potential diagnostic biomarker [13]. Other autoantibodies are nonspecific for endometriosis, but some, such as antinuclear antibodies (ANAs), have been found to the elevated in endometriosis patients [15].

Diagnosis

The diagnosis of endometriosis should be based on patient interview, examination and imaging. The importance of early disease diagnosis and treatment must be overemphasized. To reduce the negative impact on quality of life, treatment must be prompt and effective. Improving diagnosis is an important tool to reduce diagnostic delay [1].

There are several ways in which endometriosis can be diagnosed or undiagnosed. Some women experience pelvic pain, others are diagnosed during an infertility evaluation or incidentally during an unrelated pelvic surgical procedure, such as an appendectomy or tubal ligation [4].

Anamnesis plays a fundamental role, the presence or absence of certain symptoms can be very helpful in the diagnosis. The history should be based on symptoms such as dysmenorrhea, dyspareunia, dyschezia, dysuria, periovulatory pain and chronic pain; all these symptoms are a consequence of inflammatory reaction and infiltration of anatomical structures [1, 6, 10]. The most common symptoms in patients with endometriosis are dysmenorrhea (80%) and deep dyspareunia (30%) [1, 6, 10]. Symptoms occurring during puberty may be overlooked by health-care practitioners due to cultural reasons and normalization of menstrual pain [3]. Since pelvic pain is the cardinal symptom of endometriosis, the challenge is to determine whether the pain is caused by endometriosis or by other conditions. Chronic pain may also be associated with fibromyalgia and myofascial pain or with depression, past sexual abuse, adhesions, irritable bowel syndrome or interstitial cystitis. Although the presence of all these pathologies does not exclude a concomitant endometriosis [3], the pelvic examination should include a speculum examination (direct visualization of vaginal DE) and vaginal palpation [16]. The vaginal examination may be useful to look for painful hardening of the vagina, uterosacral ligaments and/or torus uterinus, and pain on mobilization of the uterus [1, 2, 10].

Transvaginal sonography (TVS) is the first-line imaging technique in the diagnosis of pelvic endometriosis especially in deep infiltrating endometriosis (DE) nodules and ovarian endometriomas (OMA) [16]. The International Deep Endometriosis Analysis has defined common criteria to standardize and reach consensus on the ultrasound diagnosis of endometriosis. The sonographic evaluation is dynamic and the pelvic organs and their mobility are assessed in real time. Bowel preparation prior to TVS improves the diagnostic accuracy of TVS in detecting DE rectosigmoid nodules [17].

Magnetic resonance imaging (MRI) is also a good tool that can be used either to examine patients with severe pain caused by TVS or to obtain further information about the lesions. In addition, sigmoid, ileocecal and urological lesions can be detected with other complementary radiological techniques [1–3].

Given the considerable advances in diagnostic imaging, exploratory laparoscopy should no longer be used to diagnose endometriotic lesions [3]. As previously explained, TVS has been shown to be accurate in the diagnosis of OMA and DE, with a higher sensitivity than diagnostic laparoscopy for rectosigmoid endometriosis.

Therapy

As with other chronic inflammatory conditions, treatment should be viewed as a long-term process. Recurrence of symptoms during drug discontinuation is normal and does not indicate hormonal manipulation is ineffective.

The available medical treatments for symptomatic endometriosis work by inhibiting ovulation, lowering serum estradiol levels and suppressing uterine blood flow [18]. The currently available first-line treatments are progestins and low-dose oral contraceptives, which are effective in two-thirds of patients. If first-line therapy does not work, there is the option of oral gonadotropin-releasing hormone (GnRH) agonists or antagonists [1]. Third line treatments include aromatase inhibitors such as letrozole.

Pain relief provided by the various drugs depends on the degree of amenorrhea achieved, high tolerability and adverse effects. Moreover, costs differ significantly. To encourage compliance, the lowest effective dose for each medication should be chosen [6]. Progestins and continuous combined contraceptives make patients amenorrheic by blocking ovulation through central inhibition of gonadotropin release. This mechanism prevents repeated menstrual reflux and has many direct effects on endometriotic implants [19]. They are effective in treating endometriosis-associated pain. The progestin component, which is predominant in modern combined contraceptives, leads to decidualization and atrophy of lesions, especially with continuous use. Progestin-only therapies include mainly medroxyprogesterone, norethisterone, dienogest, desogestrel and levonorgestrel intrauterine device [19].

Nowadays, surgery is considered a second-line treatment in most endometriosis patients. Surgical procedures may be performed laparoscopically or as an open procedure. The golden standard today is the laparoscopic approach. The goal of surgery is to remove the lesions and attempt to restore normal anatomy to reduce pain-related symptoms [20]. Excision can be performed through different techniques such as electro-excision, argon neutral plasma energy, laser energy, ultrasound scalpel or helium thermal coagulator. Patients with severe DE involving the bowel, rectum and bladder may require a multidisciplinary team involving gynecologists, general surgeons and urologists depending on the organs involved [1–3, 10].

For the treatment of chronic pelvic pain, physiotherapy and other manual techniques as well as ultrasound-guided myofascial trigger point injections may be useful in addition to endometriosis treatment [8].

Among infertile patients, the surgical treatment should be evaluated in conjunction with assisted reproductive technology, especially *in vitro* fertilization (IVF) [9, 10].

The role of IVF has grown in the years because of improvement in the safety, the high risk of surgeries and ineffectiveness of intrauterine insemination [9, 10].

Prevention

No way to prevent endometriosis is known [2]. Enhanced awareness, followed by early diagnosis and management, may slow or halt the natural progression of the disease and reduce the long term burden of painful symptoms, including possibly the risk of central sensitization, but no cure exists. Furthermore, the evidence for modifiable risk factors for endometriosis remains unacceptably sparse. Critically needed are large scale longitudinal studies that can quantify modifiable exposures in girls and young women in the pre-diagnostic, and ideally the pre-symptomatic period to determine the physiologic pathways defined by causal effects on the epigenome, transcriptome, proteome and metabolome [2, 10]. To date, few risk factors have been robustly replicated in multiple populations, with the most consistently associated with endometriosis including Müllerian anomalies, low birth weight and lean body size, early age at menarche, short menstrual cycles and nulliparity. Less research has supported associations with endocrine-disrupting toxins including diethylstilbestrol [1, 2, 4].

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Autoimmune Ovarian Insufficiency

57

Aina Borrás and Francisco Carmona

Abstract

Premature ovarian insufficiency (POI) comprises a complex disease with multiple etiopathogenic mechanisms including autoimmunity. This chapter reviews the different autoimmunity patterns related to premature ovarian aging. Some of these patterns are related to global autoimmune regulation, whereas others may be related to inflammatory autoimmunity against ovarian antigens.

Keywords

Autoimmunity · Infertility · POI · POF

Introduction

Premature ovarian failure (POF) is a dramatic disease in which young women lose their ability to become pregnant. This ovarian disorder has been defined as a continuum of decreasing ovarian function and the end of menses in women before the age of 40. So, such patients will present a progression of ovarian dysfunction preceded by a premature ovarian insufficiency (POI), that shows a hyper gonadotropic hypogonadism hormonal profile combined with, in the end, secondary amenorrhea. Most patients will present symptoms of estrogen deprivation, described below, and subfertility/infertility. Also, it is important to highlight that, in some cases, a familial history is present.

Although proper diagnostic accuracy in POI is lacking, the following diagnostic criteria and symptoms associated are frequently described [1–4]:

Diagnosis	
Premature ovarian insufficiency	
• Oligo/amenorrhea for at least 4 months	
• Elevated follicle-stimulating hormone (FSH) level >25 IU/L on 2 occasions >4 weeks apart	
Premature ovarian failure	
• Complete amenorrhea	
• FSH levels over 40 UI/L on 2 occasions >4 weeks apart	
Symptoms (*the result of estrogen deficiency*)	**Cases described**
• Vasomotor instability (hot flushes, night sweats)	40–50%
• Genitourinary syndrome	4–25%
• Mood disorders including irritability and emotional lability	45–65%
• Osteopenia and osteoporosis	30–35%

Currently, the terminology of POI is considered to better represent this premature ovarian aging condition because there is intermittent and unpredictable ovarian function and spontaneous ovulations which may end in an established ovarian failure.

The incidence of POI is estimated to be approximately 1–3% in the general female population, and 2 histological types have been described. In the first one, there is a complete absence of ovarian follicles, and it is characteristic of the disorders of sex development (DSD) where the development of chromosomal, gonadal, or anatomical sex is atypical (comprising previously called *gonadal dysgenesis* and *hermaphroditism*). In the second one, some follicles can be found, and a progression of ovarian dysfunction is observed, ending in most cases with the development of a complete absence of follicles. An intermittent and unpredictable ovarian function has been observed, and spontaneous ovulations can occur in up to 20%. In recent years, the known etiologies of POI have expanded, although the cause in most clinical cases remains undefined. POI can be iatrogenic (because of ovarian surgery, chemo-radiotherapy, etc.), caused by genetic/chromosomal aberrations, infections, environmental factors, metabolic (for example, galactosemia, etc.), endometriosis or it can be associated with autoimmune disorders [2].

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Relationship Between POI and Other Autoimmune Diseases

Autoimmunity is considered to be responsible for approximately 4–30% of POI cases. One of the reasons to suspect the autoimmune etiology is its high frequency of association with other autoimmune diseases. The most well-established autoimmune association with POI is the one linked to Addison's disease (AD), a primary autoimmune adrenal insufficiency frequently associated with multiple endocrine failure and involving high serum levels of antibodies targeted to steroid-producing cells, which is often preceded by POI. Two main types of autoantibodies are detected in patients with AD: Cy-Ad antibodies, directed against adrenal cells cytoplasm, and St-C antibodies (St-CA), which also react with a variety of steroid-producing cells, including adrenal cortex, testes, trophoblast and with different types of ovarian cells as follicular and luteal cells. Thus, 60% of patients with AD and secondary amenorrhea present St-CA, which is also present in just 15–20% of patients with AD but without amenorrhea. Furthermore, 40% of these patients will develop a POI during the next 10–15 years of follow-up [5].

As part of the diagnosis of autoimmune POI, detecting autoimmune ovarian destruction by ovarian biopsy should have been the gold standard. However, since biopsy implies an invasive procedure that can affect ovarian reserve, together with the observation that there is no proven safe and effective treatment to restore fertility in these patients, an ovarian biopsy is not recommended. Histological examination of the ovaries of POI patients with associated adrenal autoimmunity usually reveals the persistence of ovarian follicles with autoimmune oophoritis, as reflected by follicles surrounded by mononuclear inflammatory cells (plasma B and T cells) around steroid-producing cells of the pre-ovulatory follicles and corpora lutea while sparing the primordial and primary follicles. These alterations are apparent in 11% of POI patients, 78% of whom are positive for St-CA. Of notice, immunohistochemical staining demonstrates the presence of T lymphocytes (CD4+ CD8+), which is in agreement with the suggested role of T lymphocytes in ovarian autoimmunity. Moreover, perivascular and perineural inflammatory infiltrates were also reported [1].

No genetic predisposition has been shown in cases of POI associated with AD. This disease has been related to the HLA-B8/DR3 haplotype particularly with the DR B1 0301 allele, whereas POI has been related just to the HLA-A28 haplotype [6].

Some enzymes involved in steroid production may be the target for St-CA and Cy-Ad autoantibodies, particularly in the case of POI associated with AD. Such steroid cell autoantibodies show some specificity for the steroidogenic enzymes 21-hydroxylase (21OH), side chain cleavage enzyme (SCC), and 17-alpha hydroxylase (17OH) as well as NACHT leucine-rich-repeat protein 5 (NALP-5) [7, 8]. Antibodies to the FSH receptor have also been found in a small percentage of POI patients associated with AD, and antibodies from POI patients have been shown to inhibit FSH-induced DNA synthesis in ovarian tissue extracts. Zona pellucida or even luteinizing hormone receptors are other candidate autoantigens, some of which could explain the clinical features of POI. Despite these autoantibodies can be common in POI, their specificity and pathogenic effects are still questionable [9].

Furthermore, autoimmune polyglandular syndrome (APS) is a series of disorders defined as autoimmunity against endocrine organs, which is closely associated with autoimmune oophoritis. The main features of APS-I (APS type I) include Addison's disease and ovarian failure, meanwhile, APS-II is related to early gonadal failure ranging in 5–50% of patients. APS-III is one of the most common co-syndromes of POI, with a prevalence of approximately 33% in POI patients. The above results indicate that POI is strongly correlated with Addison's disease and APS and could also be considered an autoimmune disease [9].

Isolated POI

Although the frequency of concurrence with other autoimmune conditions varies somewhat between different study populations, and POI often occurs as part of an APS with high frequencies of hypothyroidism, insulin-dependent diabetes mellitus, and adrenal abnormalities, POI may also occur as an isolated ovarian-specific disorder independent of any polyglandular or global systemic autoimmune events. Thus, many cases of POI may represent a primary autoimmune ovarian abnormality, whereas other cases may represent secondary effects of a more global endocrine autoimmune dysfunction. As such, POI may have multiple distinct autoimmune manifestations perhaps dependent on the tissue distribution of the targeted autoantigen and/or the underlying specificity or lack of native immune regulatory functions. It should be noted that the pathophysiologic significance of ovarian autoantibodies and the cognate target antigen(s) that they recognize remains unclear.

Similarly, there are some signs of autoimmunity in isolated POI:

(a) Autoantibodies against other endocrine systems: autoantibodies against the thyroid are the most frequently found among patients with isolated POI (14%), autoantibodies against gastric wall cells (4%), against Langerhans cells (2%) and against the acetylcholine receptor (2%) are also frequent. However, only antibodies against Langerhans cells and acetylcholine receptors are clinically relevant. These antibodies are related to two severe diseases: diabetes mellitus type I and myasthenia gravis, respectively. Furthermore, other autoimmune diseases such as systemic lupus erythematosus have been related to POI.

(b) Antinuclear antibodies (ANA): Patients testing positive for ANA are at increased risk for developing POI; some series of cases have described that up to 20% of patients positive for ANA could develop a POI, whereas just 5% of controls would develop.

(c) Anti-DNA: Gao et al. found anti-DNA antibodies in 10% of women with POI, whereas in a control group of healthy fertile women, just 5.2% presented such antibodies [10].

(d) Antireceptor antibodies: Antireceptor antibodies are targeted against membrane hormone receptors. These antibodies may mimic the physiologic hormonal action or block the hormone function depending on their specificity and affinity. Some investigators have described the presence of antibodies directed against FSH and LH receptors in patients with POI [11–13]. However, such antibodies have also been detected in patients with iatrogenic ovarian failure.

(e) Anti-zona pellucida antibodies: This type of antibody has been described in patients with infertility of unknown origin and particularly higher levels have been also described in patients with POI. In experimental animal models, these antibodies have been able to inhibit follicular development [9].

Ovarian Histology in Patients with Isolated POI

In up to 60% of patients with isolated POI, fibrotic ovaries, without follicular presence, are observed. The number of follicles in the remaining 40% is highly variable, from a few to an almost normal amount. These patients with a normal number of ovarian follicles present gonadotrophin resistance syndrome.

Cellular Immunity Alterations in Patients with Isolated POI

Abnormalities of cellular immunity play an important role in the pathogenesis of autoimmune POI. The absolute count and percentage of peripheral blood T lymphocytes, especially CD4+ T cells, are increased in patients with POI, while the number and activity of natural killer (NK) cells seem to be reduced. POI patients present usually low levels of CD8+/CD57+ T cells (cytotoxic T lymphocytes) and an overall increase in the CD4+/CD8+ ratio [1]. However, such immune cellular alterations have also been described in patients with natural menopause, and it has been suggested that estrogen may modulate the T-cell activation arguing that this activation observed in isolated POI is the consequence of the hypoestrogenic status presented by these patients. Furthermore, hormonal replacement therapy has shown a decrease in the number of activated T cells, supporting this theory.

Occult Ovarian Insufficiency

Some patients can present infertility of unknown origin and altered ovarian reserve markers (low antimüllerian hormone levels, low antral follicular count, and elevated basal levels of FSH, usually greater than 15 UI/L), also called DOR patients (diminished ovarian reserve patients). These patients have normal menstrual cycles, but they used to have bad results in in vitro fertilization cycles with high rates of canceled cycles. It has been suggested that this reduction in ovarian reserve, associated with infertility, represents a continuum of ovarian conditions that encompass an “occult” clinical state (reduced fecundity but normal FSH levels and regular menses), “biochemical” state (reduced fecundity, altered ovarian reserve markers and regular periods) and an “overt” state, corresponding to POI [14]. There is controversy regarding whether the “occult” or “biochemical” clinical state is related also to autoimmune alterations, with no specific studies, but it should be thought that the causes that induce POI are the same that will cause these previous states of alteration in ovarian function.

Experimental Animal Models of Autoimmune Oophoritis

Several animal models of experimental autoimmune oophoritis (EAO) have been used in POI studies, with each model providing unique mechanisms for the induction of ovarian failure.

One of the classical EAO animal models includes the induction of autoimmune oophoritis in rats by immunization with rat or bovine ovarian homogenate in complete Freund’s adjuvant. In this case, inflammatory infiltrates appear in the ovaries within 14 days, and the appearance of germinal centers and increased splenic activity of both B and T cells indicates that cellular and humoral immunity are involved in this form of EAO. Serum ovarian antibodies appear after 28 days and may passively transfer decreased fertility measured by decreased litter size into naïve recipients. It is speculated that the antibodies produced in this form of EAO may mediate disease by interfering with zona pellucida antigens, thereby disrupting ovulation and/or fertilization [5].

Other experimental models of autoimmune oophoritis also include those methods that target zona pellucida; thus, immunization with heterologous zona pellucida antigens results in autoimmune oophoritis characterized by follicle depletion and ovarian failure. Immunization with zona pellucida proteins rapidly induces a marked atretic appearance and reduction, and, eventually disappearance, in the number of primary growing follicles.

Finally, other EAOs in animal models include those that develop spontaneously and lead to polyglandular abnormalities because of global immune regulatory failure after neonatal thymectomy observed in mice. Neonatal thymectomy in mice spontaneously develops autoimmune oophoritis along with autoimmune disorders of the thyroid, gut, parotid gland, and lacrimal gland within 3–14 weeks after thymectomy. This polyglandular form of oophoritis is accompanied by a loss of oocytes and the elimination of ovarian follicles. Circulating autoantibodies against oocytes, zona pellucida proteins, and steroid-producing cells appear within 4 weeks and reach their highest titers within 7–9 weeks. The inflammation subsides after 14 weeks, and the ovaries become atrophic. This type of experimental oophoritis in mice is similar to that observed in women with POI associated with Addison's disease [14].

Treatment

With all the previously mentioned physical and psychological conditions, treatment should focus on the maintenance of the patient's well-being. Hormone replacement therapy (HRT) must be performed when the diagnosis of POI is made. The estrogen deficiency in these patients is known to cause the early aging of blood vessels, bones, and other tissues and shorten patients' life expectancy.

Different fertility options will be appropriate for each individual with POI. Discussions on this topic with experienced professionals must begin not only soon after diagnosis but also throughout follow-up. Women with POI have a 5–10% chance of spontaneous conception but, on the other hand, assisted reproductive techniques with oocyte donation remain the only realistic fertility treatment for the majority of women with established POI. Donated oocytes are fertilized with the partner's sperm, and the integrity of embryos is observed. The best embryo is then chosen for implantation with the recipient that has been prepared with increasing doses of estradiol and progesterone.

Conclusion

Premature ovarian aging that ends in POI affects approximately 1–3% of women of reproductive age. Its etiopathogenic factors remain unclear in most cases but include chromosomal, genetic, enzymatic, toxic, infectious, and iatrogenic causes. An abundance of evidence indicates that autoimmunity is primarily responsible for the symptoms of a substantial cohort of POI patients mainly in cases associated with AD, APS, and oophoritis. These patients present antibodies targeted against steroid-producing cells and also antigens shared by ovarian and adrenal cells. Furthermore, the linphoplasmocitary infiltration observed around these cells in patients with POI associated with AD strongly suggests an autoimmune origin. Different animal models add also further confirmation.

Nevertheless, the evidence favoring an autoimmune origin is not so strong in patients with isolated POI, in whom some alterations on the immune cells have been described, and a greater incidence of type I diabetes and myasthenia gravis than in the general population. However, against the autoimmune origin of POI in these patients is the fact that it is very difficult to find oophoritis in cases of isolated POI.

Treatment in these cases is based on starting HRT and considering assisted reproduction techniques with gamete donation if the woman has a desire for pregnancy.

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Autoimmune Orchitis

58

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Abstract

Subacute or chronic orchitis includes mainly non-infectious etiologies and also rarely autoimmune orchitis (AO). This urological condition is characterized by testicular inflammation with the presence of antisperm antibodies leading to immobilization and/or agglutination of spermatozoa, which blocks sperm–egg contact, with consequent infertility. AO may be primary (in the absence of other autoimmune diseases) or secondary (associated with another autoimmune condition, such as IgA vasculitis, Behçet's disease, polyarteritis nodosa, IgG4-related disease, and others). This chapter reviews pathophysiology, clinical and laboratory features, diagnosis criteria, and treatment of AO.

Keywords

Orchitis · Autoimmunity/autoimmune orchitis · Male infertility

Description of Orchitis

Acute orchitis is diagnosed in patients with scrotal pain or tenderness, erythema, and testicular edema due to local or systemic infection and with a total duration of less than 6 weeks [1]. Signs and symptoms of orchitis are not specific, particularly in the context of an emergency of an acute scrotum. It is essential to distinguish testicular torsion from epididymal-orchitis, and a Doppler testicular ultrasound may help differentiate these two clinical pictures.

Subacute or chronic orchitis includes mainly non-infectious etiologies and is commonly asymptomatic, hampering the accurate diagnosis of autoimmune orchitis [2, 3]. A digital rectal exam is also relevant to exclude orchitis associated with prostatitis [1–4].

The possible role of the immune system in male reproductive tract disturbances is reinforced by the association of antisperm antibodies (ASA) and male infertility [2, 3]. In addition, there is evidence that autoimmune systemic diseases may impair testicular function, leading to gonadal dysfunction, sperm abnormalities, androgen decrease, and sperm DNA damage [4, 5].

Autoimmune orchitis is characterized by testicular inflammation with the presence of ASA. Moreover, these antisperm antibodies may induce apoptosis of spermatocytes and spermatids, leading to immobilization and/or agglutination of spermatozoa, which blocks sperm–egg contact, with consequent infertility [1–3].

Signs and Symptoms of Autoimmune Orchitis

Primary autoimmune orchitis is characterized by isolated infertility, without any specific signs or symptoms, and local or systemic concomitant conditions but associated with a marked presence of ASA in 100% of patients [2, 3].

Secondary autoimmune orchitis may be symptomatic, unilateral, or bilateral and generally occurring in the context

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Table 58.1 Signs and symptoms, associated conditions, laboratory findings, and serological markers of primary and secondary autoimmune orchitis

Autoimmune orchitis	Signs and symptoms	Associated conditions	Laboratory findings	Anti-sperm antibodies (ASA)
Primary	Isolated infertility (without any testicular signs and symptoms)	Without any local or systemic conditions	Mild to severe sperm abnormalities (low sperm count, motility, morphology, and/or sperm DNA damage), generally with normal testicular volumes and normal gonadal hormones	100%
Secondary	Acute or subacute testicular inflammation (scrotal pain/tenderness, erythema, edema and/or testicular vasculitis)	Behçet's disease, polyarteritis nodosa, IgA vasculitis (former Schönlein–Henoch purpura), IgG4-related disease, systemic lupus erythematosus, dermatomyositis, polymyositis, relapsing polychondritis, rheumatoid arthritis, systemic scleroderma, ulcerative colitis	Normal, mild to severe sperm abnormalities (low sperm count, motility, morphology and/or sperm DNA damage), generally with normal or reduced testicular volumes and normal or abnormal gonadal hormones	Not reported and up to 50%

of primary vasculitis diagnosis. The most frequent cause of secondary autoimmune orchitis is IgA vasculitis (formerly known as Henoch–Schönlein purpura), occurring mainly in children and adolescents (up to 19%), at IgA vasculitis onset in 96%, and 1% of them had acute recurrent scrotal involvement [6]. Epididymo-orchitis was reported in 8.7% of Behçet's disease [7]. This involvement was rarely identified in other systemic autoimmune diseases, such as polyarteritis nodosa, immunoglobulin G4-related disease, systemic lupus erythematosus, dermatomyositis, polymyositis, relapsing polychondritis, rheumatoid arthritis, systemic scleroderma, and ulcerative colitis [1–4, 8].

Table 58.1 illustrates the main signs and symptoms, associated conditions, laboratory findings, and primary and secondary autoimmune orchitis serological markers.

Laboratory and Imaging Findings of Autoimmune Orchitis

Commonly encountered isolated sperm abnormalities such as low sperm count, motility, and morphology can manifest in both primary and secondary autoimmune orchitis. However, these conventional semen parameters might fail to identify abnormalities in 20% of subfertile males and are considered poor indicators of fertility and pregnancy outcome [4]. The new biomarkers of spermatic function (such as sperm DNA integrity analysis), as reported in male systemic lupus erythematosus patients [5], seem to have a better diagnostic and prognostic performance for predicting male fertility potential than conventional sperm parameters.

The hypothalamus-pituitary-gonadal axis is generally not affected, and gonadal hormones (particularly FSH, LH, and morning testosterone) are usually within normal ranges in autoimmune orchitis patients [4, 5, 9]. Inhibin B is produced almost exclusively by the testes' Sertoli cells in the seminiferous tubules and may also be evaluated in men with gonadal dysfunction [9–12].

Imaging exams, particularly testicular Doppler ultrasound and magnetic resonance imaging, may be used for autoimmune orchitis diagnosis. These exams are relevant for the differential diagnosis of testicular torsion and intrascrotal testicular masses, such as abscesses, cancer, hernia, thrombosis, cysts, and hydroceles. A fine core biopsy may be required to confirm secondary autoimmune testicular abnormalities. Mild hematomas or infections were detected in less than 2% of the patients after testicular biopsies [2, 3].

Serological Markers of Autoimmune Orchitis

An immunologic basis for some cases of infertility has been identified in a significant number of infertile men, suggesting that antisperm antibodies (ASA) may have a harmful effect on fertilization. Immunologic infertility is characterized by antibodies against spermatozoa that may be detected in the serum and/or the seminal plasma or the sperm surface. Among them, the most relevant are antibodies detected in the sperm surface, especially by direct immunobead binding assay [1–3, 9]. This test detects antibodies on the sperm cell surface to the Fc portion of the ASA (sperm head, mid-piece, and/or tail) using immunobeads coated with rabbit anti-human Ig, particularly IgA, IgG, and IgM isotypes [2, 3]. The presence of multiple ASA can lead to the immobilization and/or agglutination of spermatozoa, which blocks sperm–egg interaction. They can also prevent implantation and/or arrest embryo development [13].

The serological marker of autoimmune orchitis is the presence of ASA. It is important to reinforce that at least 50% of the motile spermatozoa must be coated with immunobeads to certify the clinical importance of the ASA test. In addition, only IgG and IgA isotypes are relevant in male fertility and should be assessed by ASA assay [2, 3]. The male gonadal function impact seems to be associated with the ASA class, their quantity, specificity, and density of their coverage on the sperm cell surface [12].

Diagnostic Criteria of Autoimmune Orchitis

Autoimmune orchitis may be divided into primary and secondary based on the presence or absence of signs and symptoms, associated diseases, laboratory findings, and serological markers. The diagnostic criteria of these two organ-specific conditions are illustrated in Table 58.1.

Primary autoimmune orchitis is characterized by isolated infertility and autoantibodies directed to sperm without any evidence of systemic autoimmune disease. An immunologic basis for some cases of infertility has been identified in approximately 10% of infertile men, suggesting that ASA may have a harmful effect on fertilization [12].

The secondary autoimmune orchitis is manifested by orchitis and/or testicular vasculitis, and it is uniformly associated with a systemic autoimmune disease. The most frequent chronic conditions associated with this autoimmune orchitis subtype are IgA vasculitis (former Schönlein–Henoch purpura), Behçet's disease, polyarteritis nodosa, IgG4-related disease, systemic lupus erythematosus, dermatomyositis, polymyositis, relapsing polychondritis, rheumatoid arthritis, systemic scleroderma, and ulcerative colitis. The overall frequency of acute orchitis in rheumatic diseases is low [1–3].

The frequencies of acute orchitis and ASA in autoimmune rheumatic diseases are 2–31% and 0–50%, respectively [1–3]. The most frequent autoimmune rheumatic disease associated with ASA antibodies (13–50%) was systemic lupus erythematosus, without a clear association with infertility. Indeed, we previously reported a 40% ASA by direct Immunobead test, using Immunobead rabbit anti-human Ig (IgA, IgG, and IgM) kits in male systemic lupus erythematosus patients. The presence of these antisperm antibodies was not associated with gonadal dysfunction parameters and immunosuppressive drug therapy [14].

Common causes of ASA include previous genital tract infection, surgical trauma to testes or scrotum (therapeutic or iatrogenic) such as testicular biopsy, varicocele, testicular trauma, testicular torsion, testicular cancer, vasectomy, and other obstructions [1–3]. Patients with a history suggesting the above conditions are candidates for ASA testing [15].

Pathogenesis of Autoimmune Orchitis

Although testis has a privileged immune condition, it is not inaccessible to the immune system. Experimental autoimmune orchitis (EAO) is a useful experimental model for this organ-specific condition [16]. The main target of EAO models is the germ cells responsible for spermatogenesis, mainly spermatocytes and spermatids cells, undergoing apoptosis and sloughing [1–3]. Progression of EAO is also associated with increased testicular endothelial cells and interstitial testicular blood vessels, suggesting an angiogenic process [16]. Models of EAO may show responses similar to observations in patients after testicular extraction for mixed atrophy of spermatogenesis, particularly peritubular lymphocytic infiltrates, thickening of the *lamina propria*, autoantibodies, or secretion of mediators [17].

Mediators promoted by inflammation, infection, or trauma on testicles may induce T cell response with high levels of pro-inflammatory cytokines (such as IFN-γ, IL-1, IL-6, IL-12, IL-17, and IL-23), increased permeability of blood–testis barrier, and significantly triggering ASA, spermatocytes, and spermatids apoptosis or vasculitis. ASA may produce spermatozoa agglutination, sperm-cell immobilization, and sperm–oocyte interaction during fertilization. More recently, high intratesticular nitric oxide (NO) levels were also related to limited germ cell proliferation [18].

Implications of combined pathogenic pathways are vasculitis, sperm dysfunction, increase of seminal reactive oxygen species (ROS), and sperm DNA damage, leading to infertility [1–3] (Fig. 58.1).

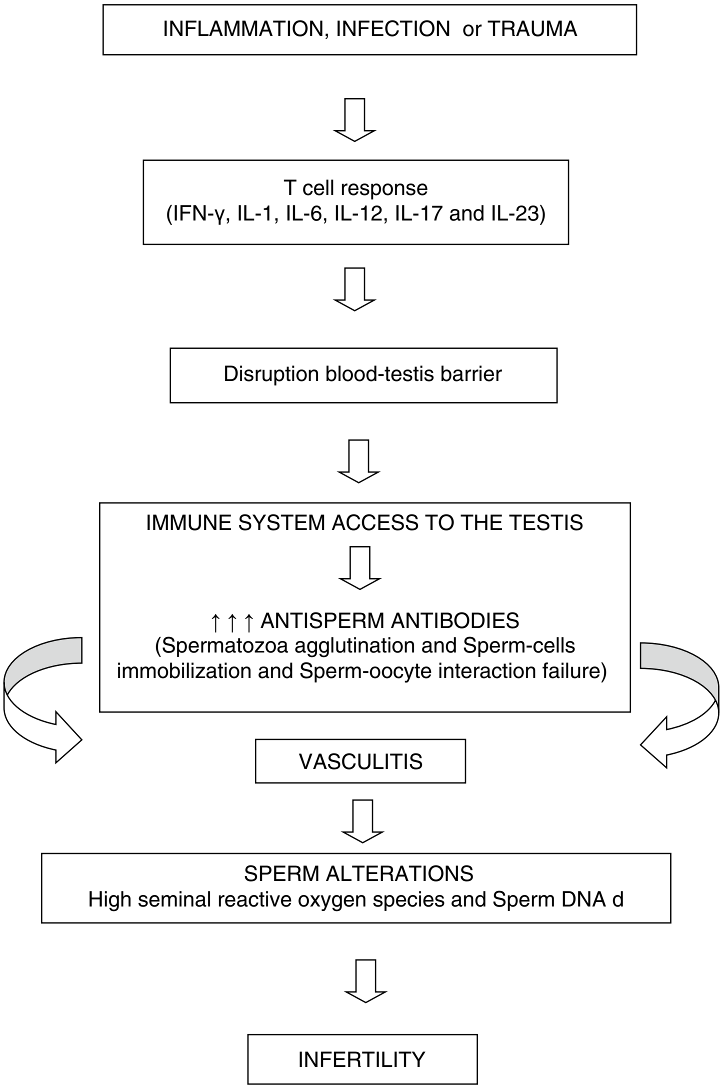
INFLAMMATION, INFECTION or TRAUMA
T cell response
(IFN-γ, IL-1, IL-6, IL-12, IL-17 and IL-23)
Disruption blood-testis barrier
IMMUNE SYSTEM ACCESS TO THE TESTIS
↑↑↑ ANTISPERM ANTIBODIES
(Spermatozoa agglutination and Sperm-cells immobilization and Sperm-oocyte interaction failure)
VASCULITIS
SPERM ALTERATIONS
High seminal reactive oxygen species and Sperm DNA d
INFERTILITY

Fig. 58.1 Pathogenesis of autoimmune orchitis

Therapy and Prevention of Autoimmune Orchitis

The treatment of acute orchitis includes analgesics, local cooling, rest, and scrotal elevation. Nerve block may be indicated as an invasive painkiller method with 5 ml of 1% lidocaine nearby the spermatic cord and may be helpful in patients with severe pain [1–3].

Secondary autoimmune orchitis is treated with immunosuppressive or biologics drugs, particularly glucocorticoid, azathioprine, intravenous cyclophosphamide, and intravenous immunoglobulin [1–3, 6, 14].

The real significance of ASA in infertile men is controversial, and currently, there are no standardized treatment regimens. Oral corticoids are commonly used to suppress antibody production, but no double-blind, randomized trial has confirmed their efficacy to date. A previous report showed a significant increase in pregnancy rates in males receiving prednisolone (20 mg twice daily on days 1–10 of the female partner's menstrual cycle, followed by 5 mg on days 11 and 12) for more than 3 months compared to placebo [19]. Assisted reproductive technology, particularly intracytoplasmic sperm injection (ICSI), seems to be the best option for male infertility with the presence of ASA. ICSI is indicated in patients with ASA and severe sperm autoimmunity, mainly in infertile males with low sperm count and motility [2].

Future perspectives in the clinical practice of autoimmune orchitis patients include analysis of sperm function tests, particularly ROS measurement, sperm DNA damage, and whole genomic analysis of spermatozoa [2].

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Part VI

Hepatobiliary and Pancreatic Autoimmune Diseases

Autoimmune Hepatitis

59

Maria-Carlota Londoño and Sergio Rodríguez-Tajes

Abstract

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease. It can lead to cirrhosis, liver dysfunction, hepatocellular carcinoma and death if left untreated. Its clinical presentation is exceedingly variable ranging from asymptomatic to fulminant hepatitis with liver failure. AIH diagnosis is based on the presence of clinical, biochemical, serological and histological criteria, although none of these are disease-specific; thus, other causes of liver disease must be ruled out. Several scoring systems have been created to facilitate and standardize AIH diagnosis. In this chapter, we shall review previous criteria as well as contemporary literature to provide methods for improving serological and histological criteria.

Keywords

Autoimmune hepatitis · Scoring system · Diagnostic criteria · Liver biopsy · Autoantibodies

Introduction

Autoimmune hepatitis (AIH) is a rare chronic inflammatory disease of the liver affecting 16–18 cases per 100,000 inhabitants in Europe. It is characterized by an increase in transaminases and IgG levels, circulating autoantibodies and typical histological features (portal inflammatory infiltrate and interface hepatitis). AIH affects predominantly women at all ages, but it has two peaks of incidence, one in puberty and the other between fourth and sixth decades of life [1, 2]. The disease can be classified in type 1 and type 2 according to the presence of certain autoantibodies. Type 1 AIH is the most common form of AIH and is defined by the presence of antinuclear (ANA) and/or anti-smooth muscle (ASMA) antibodies. Approximately, 7–22% of patients with type 1 AIH have positive anti-soluble liver antigen (anti-SLA) antibodies. They are highly specific (99%) for AIH and are associated with a more severe course of the disease. These patients were initially classified as type 3 AIH, but currently it is considered as a subgroup of type 1 AIH with longer time to achieve remission and a higher probability of relapse after immunosuppression withdrawal. Type 2 AIH occurs in 5–10% of patients, children and young adults. It is typically characterized by the presence of anti-liver kidney microsomal antibodies (anti-LKM) and its association with an aggressive disease [3].

Despite being considered a rare disease (ORPHA:2137), the epidemiology of AIH has significantly changed with increasing incidence and prevalence in Europe, especially in women older than 65 years [4]. This is probably related to environmental factors such as better living conditions and changes in lifestyle and diet that modulate gut microbiome. The pathogenesis of the disease is not very well know, but current evidence suggests an interaction between genetic and environmental factors. AIH is associated with HLA class II, especially DRB1*0401 and DRB1*0301. Polymorphisms in non-HLA genes (*TLA-4*, TNF-α, vitamin D receptor [*VDR*], SH2B adapter protein 3 [*SH2B3*] and caspase recruitment domain family member 10 [*CARD10*]) have also been described but the risk is lower. Exposure to virus, drugs, herbal products and others plays an important role in modulating the immune system and inducing the loss of tolerance to self-liver antigens [5].

The spectrum of the disease is extremely heterogeneous ranging from an asymptomatic course to an acute hepatitis with a fulminant course. The clinical phenotypes of AIH are shown in Table 59.1.

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Table 59.1 Clinical presentation of autoimmune hepatitis

Presentation	Characteristics
Chronic AIH	– Most common clinical presentation – Non-specific symptoms → fatigue, right upper quadrant pain, anorexia, weight loss, polyarthralgia – Commonly associated with other autoimmune diseases
Acute	– 25% of patients – Acute exacerbation of a chronic AIH or true acute presentation – Jaundice, nausea, vomiting, right upper quadrant pain
Asymptomatic	– 24–35% – Abnormal liver tests – Develop symptoms after 2–120 months – Fluctuating course with spontaneous improvement in liver tests

Diagnostic Criteria

The diagnosis of AIH is based on the presence of clinical, biochemical, serological and histological criteria, after the exclusion of other causes of liver disease including viral hepatitis, Wilson disease, drug (or herbal)-induced liver injury (DILI) and metabolic dysfunction-associated steatotic liver disease (MASLD) [1, 6].

To facilitate and standardize the diagnosis of AIH, the International Autoimmune Hepatitis Group (IAIHG) developed a diagnostic scoring system in 1993, subsequently revised in 1999 [7] (Table 59.2) and simplified in 2008 [8] (Table 59.3). The simplified scoring system requires four variables, autoantibodies, IgG levels, histology and the exclusion of viral hepatitis. This score has lower sensitivity (95% vs. 100%) and higher specificity (90% vs. 73%) and accuracy (92% vs. 82%) than its predecessors, but still fails to identify atypical cases (AIH with characteristics of primary biliary cholangitis, primary sclerosing cholangitis and/or MASLD) and those presenting with an acute hepatitis. Therefore, clinical practice guidelines recommend the use of the revised criteria for patients with unusual or complex features and those with clinical suspicion of AIH and low simplified score [1–3].

Despite these recommendations, scoring systems need to be redefined and validated in larger populations with different phenotypes of AIH. In this sense, the IAIHG and the ERN-LIVER (European Reference Network in Hepatological Rare Diseases) have been working to generate more evidence to improve the accuracy of two of the most important diagnostic criteria, autoantibodies and histological features [9–11].

Table 59.2 Revised scoring system for the diagnosis of autoimmune hepatitis

Characteristic	Points
Female sex	+2
ALP/AST ratio	
>3	−2
1.5–3	0
<3	+2
IgG x ULN	
1–1.5	+1
1.5–2	+2
>2	+3
ANA, ASMA, anti-LKM	
1:40	+1
1:80	+2
>1:80	+3
Hepatotoxic drugs	
Yes	−4
No	+1
Alcohol intake	
>60 g/day	−2
<25 g/day	+2
Histological findings	
None of the following	−5
Biliary changes	−3
Rosette formation	+1
Lymphoplasmacytic infiltrate	+1
Other changes	+2
Interface hepatitis	+3
Other autoimmune disease	+2
AMA positivity	−4
Other autoantibodies (anti-SLA, anti-LC1, ANCAS)	+2
HLA DR3 or DR4	+1
Viral hepatitis markers	
Positive	−3
Negative	+3
Response to immunosuppression	
Remission	+2
Remission without relapse	+3
Pretreatment aggregate score	Posttreatment aggregate score
Definite >15	Definite >17
Probable 10–15	Probable 12–17

ALP alkaline phosphatase, *AST* aspartate aminotransferase, *IgG* immunoglobulin G, *ULN* upper limit of normal, *ANA* antinuclear antibodies, *ASMA* anti-smooth muscle antibodies, *anti-LKM* anti-liver kidney microsomal antibodies, *AMA* anti-mitochondrial antibodies, *anti-SLA* anti-soluble liver antigen antibodies, *anti-LC1* anti-liver cytosol 1 antibodies, *ANCA* anti-neutrophil cytoplasmic antibodies, *HLA* human leucocyte antigen

Table 59.3 Simplified scoring system for the diagnosis of autoimmune hepatitis

Characteristic	0 points	1 point	2 points
Autoantibodies			
ANA[a] or ASMA[a] or	Negative	≥1:40	≥1:80
Anti-LKM or			≥1:40
Anti-SLA			Positive
IgG	Normal	>ULN	>1.1 x ULN
Viral hepatitis	Positive		Negative
Liver biopsy	Atypical[d]	Compatible[c]	Typical[b]
Definite ≥7			
Probable ≥6			

IgG immunoglobulin G, *ULN* upper limit of normal, *ANA* antinuclear antibodies, *ASMA* anti-smooth muscle antibodies, *anti-LKM* anti-liver kidney microsomal antibodies, *AMA* anti-mitochondrial antibodies, *anti-SLA* anti-soluble liver antigen antibodies

[a] In case that ANA or ASMA were determined by IIF in HEp-2 (and not in frozen rodent tissue), the score will give 1 point to a titer ≥1:80 to 1:160, and 2 points to a titer ≥1:160 to 1:320

[b] Typical: interface hepatitis, lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into the lobule, emperipolesis and hepatic rosette formation

[c] Compatible: chronic hepatitis with lymphocytic infiltration without all the features considered typical

[d] Atypical: showing signs of another liver disease

Autoantibodies

The presence of positive autoantibodies, ANA, ASMA, anti-LKM and anti-SLA, is one of the key components of the diagnostic scoring systems. However, most of them are not specific of AIH and can also be positive in patients with other liver diseases such as viral hepatitis, DILI, MASLD and even Wilson disease. Moreover, the sensitivity of ANA, ASMA and anti-LKM for the diagnosis of AIH is 32%, 16% and 1%, respectively. As a result, their diagnostic accuracy is around 50–60% [3].

Screening of autoantibodies is usually performed by indirect immunofluorescence (IIF) on frozen rodent tissues sections with a cutoff titer of 1:40 considered as positive in AIH scoring systems. However, several laboratories determine autoantibodies by ELISA or IIF on human epithelioma cells (HEp-2) cells, for which the scores do not account for. HEp-2 cell substrates have higher sensitivity for the determination of ANA and ASMA and the cutoff titer needs to be adjusted, but this is not considered in the current diagnostic scoring systems. A recent study compared the sensitivity of ANA and ASMA determined by IIF in frozen rodent tissue and HEp-2 cells, to establish the cutoff titer in each technique that allows the implementation of IIF on HEp-2 cells in the scoring system. The authors found that an ANA cutoff titer of 1:160 on HEp-2 IIF had a similar sensitivity and specificity as a cutoff titer of 1:40 on frozen liver tissue (75% and 74% vs. 84% and 70%, respectively). Similar results were obtained when ASMA antibodies were analyzed [10].

IIF, however, is time-consuming and requires experienced personnel. Therefore, ELISA has emerged as a new alternative for antibody testing, but it lacks standardization and could potentially miss ANA positive patients who do not react to known nuclear antigens. In the previously mentioned study, different ELISA kits for the quantification of ANA and ASMA were compared to IIF. ELISA performed well with areas under de receiver operator curve (ROC) ranging from 0.70 to 0.88 for the prediction of AIH and is a potentially good alternative of IIF. However, its performance varies greatly, and the cutoffs need to be validated. Based on this study, the authors proposed a modification of the simplified scoring system implementing different cutoff titers according to the technique used to determine autoantibodies (Table 59.3) [9, 10].

Finally, it is important to consider that up to 30% of patients with AIH, especially those with an acute presentation can present with negative autoantibodies. The pathogenic mechanisms of seronegative AIH are the same as described for classic AIH, but it has been proposed that the antigen–antibody interaction and formation of immunocomplexes could be the reason for the lack of autoantibody detection. This theory is sustained by the emergence of autoantibodies later during the disease. It is also possible that patients with seronegative AIH have unknown antibodies not detected with current technology. Therefore, in patients with seronegative AIH, the response to corticosteroid treatment is fundamental to confirm the diagnosis [12].

Histology

Liver biopsy is essential for the diagnosis of AIH and serves, not only to confirm the diagnosis, but also to rule-out other causes of liver dysfunction and fibrosis staging. As shown in Table 59.3, the simplified scoring system gives three points to the presence of typical histological features defined by lymphoplasmacytic portal infiltrate, interface hepatitis, emperipolesis and rosette formation. However, none of these characteristics are specific of AIH [8]. In addition, patients with acute AIH frequently lack these features and present with lobular inflammation (or necrosis) and central perivenulitis which sometimes is accompanied by a plasma-cell rich infiltrate [13]. Yet, none of these histological lesions are included in the diagnostic criteria. Moreover, AIH can occur in patients with other liver diseases, especially MASLD, and current criteria established that the presence of histological characteristics of other liver disease is an atypical presentation eliminating the possibility of giving a definitive diagnosis of AIH.

Therefore, a recent consensus proposes to stratify liver biopsy as follows: (1) Likely AIH if the patient presents more than mild interface hepatitis and/or more than mild lobular hepatitis, (2) Possible AIH in patients showing portal lymphoplasmacytic infiltrate (without the other "likely" features) and no signs of other liver disease. In patients with signs of other liver disease, the presence of interface hepatitis and/or more than mild lobular hepatitis is mandatory, and (3) Unlikely AIH when histological features suggestive of another liver disease are present and the "likely" features of AIH are absent. In patients with an acute presentation, the interpretation of the liver biopsy is challenging because the liver damage is mainly located in the centrilobular area. In these patients, the presence of lobular hepatitis, central perivenulitis and plasma cell groups with or without portal inflammation are the main histological findings [11]. This proposal needs to be validated in collaborative prospective studies.

Therapy

The goal of therapy in patients with AIH is to achieve complete biochemical response (CBR), defined as the normalization of transaminases and IgG levels 6 months after treatment initiation [14]. This is usually followed by histological remission but in clinical practice a liver biopsy to confirm it, is not routinely performed. CBR halts fibrosis progression and, in some cases, also induce fibrosis regression. The first-line treatment consists in the administration of corticosteroids (generally predniso(lo)ne 0.5–1 mg/kg/day) to induce remission and azathioprine (AZA, 1–2 mg/kg/day) as maintenance treatment [1, 2]. The dose of prednisone should be progressively tapered (10 mg/week until 20 mg/day, 5 mg/week until 10 mg, and then 2.5–5 mg/1–2 months) aiming to achieve complete corticosteroid withdrawal after 6–12 months of treatment. The use of budesonide (9 mg/day) as an alternative to predniso(lo)ne is recommended in clinical practice guidelines [6], but a recent large multicenter retrospective study comparing budesonide and predniso(lo)ne in treatment-naïve patients shows significantly slower and lower response rates in patients treated with budesonide [15]. In addition, budesonide is not recommended in patients with cirrhosis or those with an acute presentation due to the risk of side effects related to the first pass in the liver.

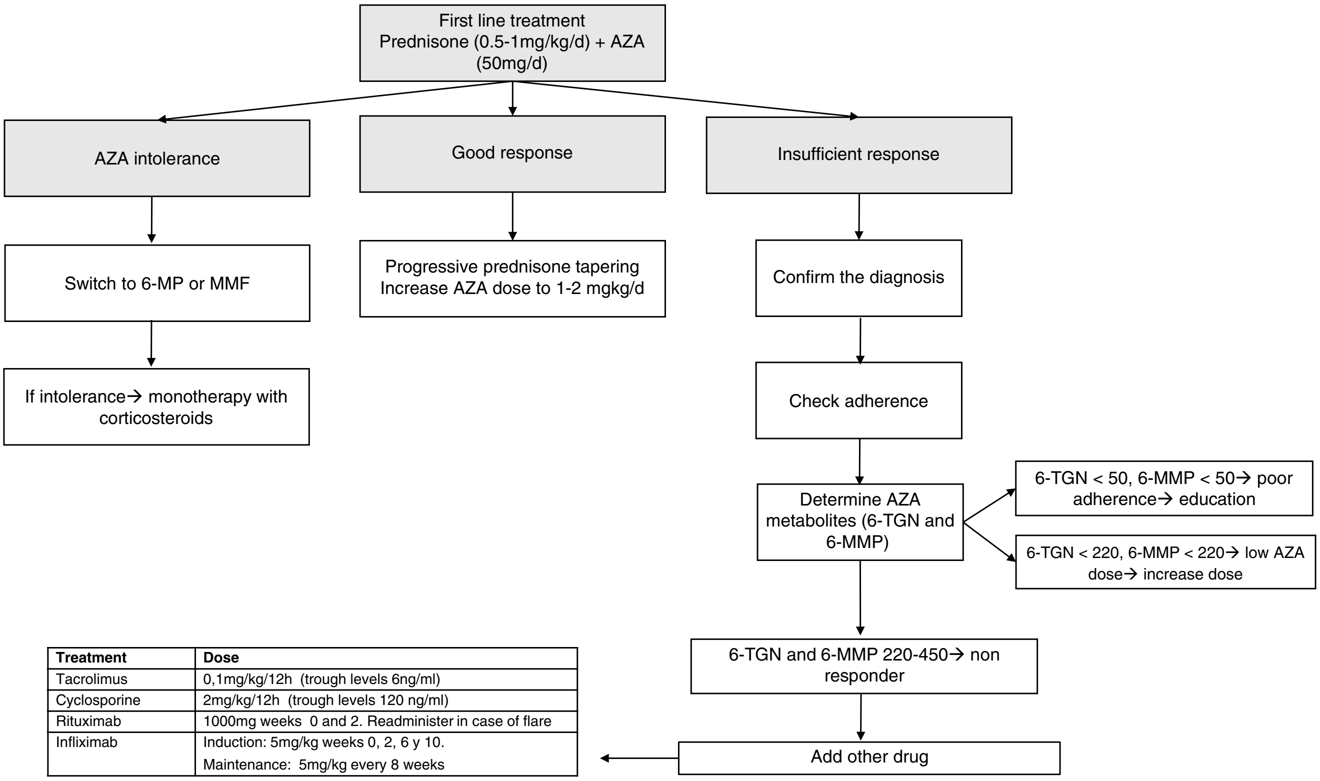
The combination of corticosteroids and AZA yields a response rate ranging between 44% and 100% depending on the study and the definition of response. However, approximately one-third of patients require ≥10 mg of prednisone to maintain disease remission. This is clearly suboptimal because the long-term use of corticosteroids at high dose is associated with a significant number of adverse events [16].

More recently, mycophenolate (MMF) has been proposed as an alternative to AZA based on a high rate of CBR obtained in treatment-naïve patients and low rate of adverse events or intolerance. A prospective propensity matching trial of MMF vs. AZA as first-line treatments found that MMF was associated with higher rates of CBR, even when patients who were intolerant or unresponsive to AZA were included in the analysis [17]. Furthermore, preliminary results from the unique controlled randomized trial of AZA vs. MMF (CAMARO trial) for the induction of response in treatment-naive AIH patients showed that MMF was superior in the changes of achieving CBR at 6 months (56.4 vs. 29%; $p = 0.02$) with significantly lower adverse events [18]. More data are needed to confirm these results, but they will probably change future clinical practice guidelines.

Approximately 25% of patients are intolerant to AZA, most of them presenting gastrointestinal symptoms, rash, fever or arthralgia. The most dangerous side effect of AZA is bone marrow toxicity. Although very rare (0.3–0.5%), guidelines recommend monitoring the activity of enzyme thiopurine methyl transferase to detect patients with zero or low enzyme activity and therefore a high risk of toxicity. In patients with AZA intolerance, a second-line treatment with 6-mercaptopurine or MMF serve as good alternatives, but this recommendation is based on case series or retrospective studies [12, 19].

Finally, 15–20% of patients do not meet the criteria of CBR and are considered as patients with insufficient response. In these patients, it is necessary to confirm the diagnosis and assure treatment adherence. The determination of AZA metabolites, 6-thioguanine (6-TG) and 6-methyl mercaptopurine (6-MMP) can help to determine low adherence, low dose or altered AZA metabolism, and to adjust the dose of AZA. In case of insufficient response and adequate levels of 6-TG and 6-MMP, multiple options have been investigated [9, 20]. However, the lack of randomized clinical trials and/or head-to-head studies hiders any recommendation and encourage to refer these patients to expert centers. Figure 59.1 shows the current treatment strategy for the management of AIH. Most commonly used therapies for patients with insufficient response are tacrolimus, rituximab or infliximab. MMF could also be attempted, but its efficacy in patients with insufficient response appears to be lower than other options.

Clinical practice guidelines recommend continuing immunosuppressive treatment for at least 2 years after CBR. Then, complete immunosuppression withdrawal could be attempted, but the risk of relapse is elevated, and a close follow-up of these patients is mandatory [2].


First line treatment
Prednisone (0.5-1mg/kg/d) + AZA (50mg/d)
AZA intolerance
Good response
Insufficient response
Switch to 6-MP or MMF
Progressive prednisone tapering
Increase AZA dose to 1-2 mgkg/d
Confirm the diagnosis
If intolerance→ monotherapy with corticosteroids
Check adherence
Determine AZA metabolites (6-TGN and 6-MMP)
6-TGN < 50, 6-MMP < 50→ poor adherence→ education
6-TGN < 220, 6-MMP < 220→ low AZA dose→ increase dose
6-TGN and 6-MMP 220-450→ non responder
Add other drug

Treatment	Dose
Tacrolimus	0,1mg/kg/12h (trough levels 6ng/ml)
Cyclosporine	2mg/kg/12h (trough levels 120 ng/ml)
Rituximab	1000mg weeks 0 and 2. Readminister in case of flare
Infliximab	Induction: 5mg/kg weeks 0, 2, 6 y 10. Maintenance: 5mg/kg every 8 weeks

Fig. 59.1 Strategies for the management of patients with autoimmune hepatitis. *ZA* azathioprine, *6MP* 6-mercaptopurine, *MMF* mycophenolate, *6-TG* 6-thioguanine, *6-MMP* 6-methyl mercaptopurine

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Primary Biliary Cholangitis

60

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Abstract

Primary biliary cholangitis (PBC) is a chronic, female-predominant cholestatic liver disease characterized by autoimmune-mediated destruction of small- to medium-sized intrahepatic bile ducts, elevated alkaline phosphatase levels, and the presence of high-titer anti-mitochondrial autoantibodies (AMA). Anti-gp210, anti-Sp100, anti-Kelch, and anti-hexokinase can also be detected in both AMA positive and AMA negative PBC patients. The laboratory and serological markers as well as criteria for the clinical diagnosis of PBC have been well established. However, the clinical course of PBC is heterogeneous with variable response to drug therapy. Ursodeoxycholic acid (UDCA) and obeticholic acid (OCA) are currently employed as first- and second-line treatments, respectively. Here, we discuss the key criteria for clinicians in diagnosing PBC, focusing on clinical and biochemical abnormalities, immunological parameters, liver pathology, and the importance of distinguishing PBC from other causes of cholestatic disease. Finally, we discuss current approaches to preventing disease progression, treatment, and highlight recent advances in mechanism-based target therapies for PBC, as well as potential therapeutic strategies to enhance the efficacy of existing treatments.

Keywords

Interlobular bile ducts destruction · Non-suppurative destructive cholangitis · Anti-mitochondrial autoantibodies · Sera biochemistry · Florid duct lesions · Ursodeoxycholic acid · Obeticholic acid · Mechanism-based target therapies

Description of the Disease

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease presented with autoimmune-mediated destruction of small- to medium-sized intrahepatic bile ducts with typical histopathology of chronic non-suppurative destruction of small- or medium-sized cholangitis, leading to liver fibrosis and cirrhosis [1]. Immunologically, PBC is characterized by an articulated immunologic response that involves both humoral and cellular responses against mitochondrial autoantigens, with the E2 component of the pyruvate dehydrogenase complex (PDC-E2) identified as the major autoantigen. Biliary epithelial cells have often been considered a passive target of the immune attack in PBC. However, cholangiocytes dedifferentiation, senescence, stress and DNA damage have been recognized to play an active role in the pathogenesis of PBC [2].

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PBC presents a striking female preponderance. However, the disease seems to be more aggressive in males and with worse prognosis. The global prevalence of PBC is estimated at 14.6 per 100,000 population, ranging from 1.91 to 40.2 [3]. Both the incidence and prevalence of this condition are increasing, with the Asia-Pacific, Europe and North America reporting annual incidences of 0.84, 1.86 and 2.75 per 100,000 population, respectively [4]. There are also reports of slight smoothing of sex differences in PBC.

The clinical course of the disease is insidious and heterogeneous with variable individual responses to drug therapy. Ursodeoxycholic acid (UDCA) and obeticholic acid (OCA) are currently used as first- and second-line treatments, respectively. However, many patients do not respond adequately to UDCA, and the long-term effects of these drugs are limited. There is strong evidence for the interplay of genetic, epigenetics and environmental factors driving individual host susceptibility. These studies have delineated key environmental factors and cellular pathways involved in the pathophysiology of the disease. Although large-scale GWAS performed have identified a number of non-HLA loci associated with PBC susceptibility**.** However, these loci are non-PBC specific, and most of the identified non-HLA loci have also been found to be susceptible gene loci in other autoimmune diseases and different between populations.

Signs and Symptoms of PBC

The most common symptoms in patients with PBC are fatigue (65%) and itchiness (55%). Other symptoms may include abdominal discomfort and joint pain. At later stage of disease, patients can also be presented with hypercholesterolemia, jaundice, dry eyes and mouth (sicca syndrome). Asymptomatic patients with elevated alkaline phosphatase should be further elevated by serological autoantibody analysis, liver function test and liver biopsy for further diagnosis.

Laboratory and Serological Markers in PBC

Serological samples with elevation in liver biochemical parameters, IgG, IgM and bilirubin are suspected for PBC (Table 60.1) and are further evaluated by autoantibodies detection. Over 95% of PBC patients are positive for anti-mitochondrial autoantibodies (AMA). Anti-gp210, anti-Sp100, anti-Kelch and anti-hexokinase can also be detected in both AMA-positive and AMA-negative PBC patients (Table 60.2).

Table 60.1 Liver biochemistry and serological markers in PBC

Liver biochemistry test
Alkaline phosphatase (ALP): elevated
Alanine transaminase (ALT): elevated
Aspartate aminotransferase (AST): elevated
Gamma-glutamyltransferase (GGT): elevated
Serological markers
IgM and IgG: elevated
Serum bilirubin: elevated

Table 60.2 Frequency of PBC-associated autoantibodies in AMA-positive and AMA-negative PBC patients

Antibody	AMA+ (%)	AMA− (%)
AMA	100	0
Anti-gp210	16–18	15–45
Anti-Sp100	21–31	13–54
Anti-kelch	19–26	10–29
Anti-hexokinase	39–50	12–40

Diagnostic Criteria of PBC

The clinical diagnosis of PBC has been well established according to the guidelines from the American Association of Liver Diseases and the European Association of Liver Diseases [5, 6]. At least two of the following must be present for a confirmed diagnosis:

- Alkaline phosphatase levels: at least 1.5 times the upper limit of normal.
- Presence of AMA with a titer of 1:40 or higher by immunofluorescence. If AMA is negative, other PBC-specific autoantibodies (such as sp100 or gp210) can be considered.
- Histological data: non-suppurative destructive cholangitis and destruction of interlobular bile ducts. Additionally, there should be no extrahepatic biliary obstruction and comorbidities affecting the liver of the patient.

Here, we will describe the when and how in the diagnosis of PBC.

When to Consider PBC?

PBC should be suspected in patients with persistent elevation of cholestatic liver enzymes in serum liver tests without extrahepatic biliary obstruction, or symptoms including unexplained itching, fatigue, jaundice, sicca complex, unintentional weight loss or right upper quadrant discomfort. Other associated conditions may increase the likelihood of

PBC, such as Sjögren's syndrome, arthritis and Raynaud's phenomenon.

How to Diagnose PBC?

Clinical and Biochemical Abnormalities

The main clinical characteristic feature of PBC is cholestasis. Cholestasis derived from the impairment of bile formation and/or bile flow, with the symptoms ranging from asymptomatic to distinct symptoms including fatigue, cholestatic pruritus and jaundice. In the initial stages, patients are usually asymptomatic, elevated levels of serum ALP and GGT are observed as early biochemical markers. As the condition progresses, there is an onset of conjugated hyperbilirubinemia. Cholestasis can be classically classified as chronic if it persists for more than 6 months [5]. It can be categorized as intrahepatic or extrahepatic and can manifest as hepatocellular or cholangiocellular forms of impaired bile formation. Jaundice, also known as icterus, which is characterized by yellow discoloration of the skin, sclera and mucous membranes, is caused by hyperbilirubinemia. It could indicate severe cholestasis but can also be caused by pre-, intra- and post-hepatic factors.

Patients with elevated ALP levels and/or suggestive symptoms should be further examined and evaluated by performing hepatobiliary imaging to exclude extrahepatic biliary obstruction. Usually, a right upper quadrant ultrasound is performed while magnetic resonance cholangiopancreatography (MRCP) is also a safe and accurate imaging method for evaluating the intra- and extrahepatic biliary tree in cholestatic patients when primary sclerosing cholangitis is suspected. If there is a high suspicion of obstruction, endoscopic retrograde cholangiopancreatography (ERCP) may be recommended.

Immunological Abnormalities

For patients with chronic intrahepatic cholestasis, the recommended next diagnostic step is to determine serum AMA and PBC-specific ANA (by immunofluorescence) and/or antigen specific anti-sp100/anti-gp210 testing via Western blotting or enzyme-linked immunosorbent assay (ELISA) [7, 8]. AMA, directed to the E2-subunit of the pyruvate dehydrogenase complex (PDC-E2), are considered the serological hallmark of PBC and are present in around 95% of PBC patients [9]. The majority of assays exhibit a sensitivity of 95% and specificity of 98% for PBC [10]. AMA reactivity combined with abnormal serum liver tests is sufficient to diagnose PBC. ANA are detected in up to 70% of patients with PBC [11]. There are several staining patterns that may be observed, including two immunofluorescence patterns that are considered "PBC-specific": the multiple nuclear dots pattern (target antigen, Sp100) and the rim-like/membranous pattern (target antigens, gp210, nucleoporin p62 and the lamin B receptor) [12]. Additionally, other antibodies like anticentromere, anti-SSA/Ro and anti-dsDNA antibodies may also be detected in PBC.

Histologic Abnormalities

A liver biopsy should be considered if the diagnostic measures described above fail to identify the cause of chronic intrahepatic cholestasis, or when co-existent autoimmune hepatitis (AIH) or non-alcoholic steatohepatitis (NASH) is suspected. Although a liver biopsy may not be essential for diagnosing PBC, it can offer valuable insights into staging and prognosis. A liver biopsy is typically performed in cases where the diagnosis is uncertain, e.g., the patient shows signs of AIH (such as elevated serum ALT and anti-smooth muscle antibodies), or if the patient does not respond adequately to ursodeoxycholic acid therapy.

The pathognomonic pathology of PBC is chronic non-suppurative inflammation that surrounds and destroys interlobular and septal bile ducts, also known as "florid duct lesions." Histologic findings in PBC are commonly classified on a scale of one to four for staging purposes (Fig. 60.1).

Stage 1: Inflammation and/or abnormal connective tissue confined to the portal areas
Stage 2: Inflammation and/or fibrosis in portal and periportal areas
Stage 3: Bridging fibrosis and ductopenia
Stage 4: Cirrhosis

What to Differentiate from PBC?

Other causes of cholestasis should be considered in the differential diagnosis of PBC. The other causes are listed in the following:

Bile duct obstruction from gallstones or malignancy
Primary sclerosing cholangitis (PSC)
IgG4-related disease
Drug-induced cholestasis
Sarcoidosis
Bacterial, fungal and viral infections
Hepatic amyloidosis
Lymphoma and solid organ malignancies
Endocrine dysfunction
Cardiac diseases
Intrahepatic cholestasis of pregnancy
Total parenteral nutrition
Viral hepatitis
Graft Versus Host Disease (GVHD)

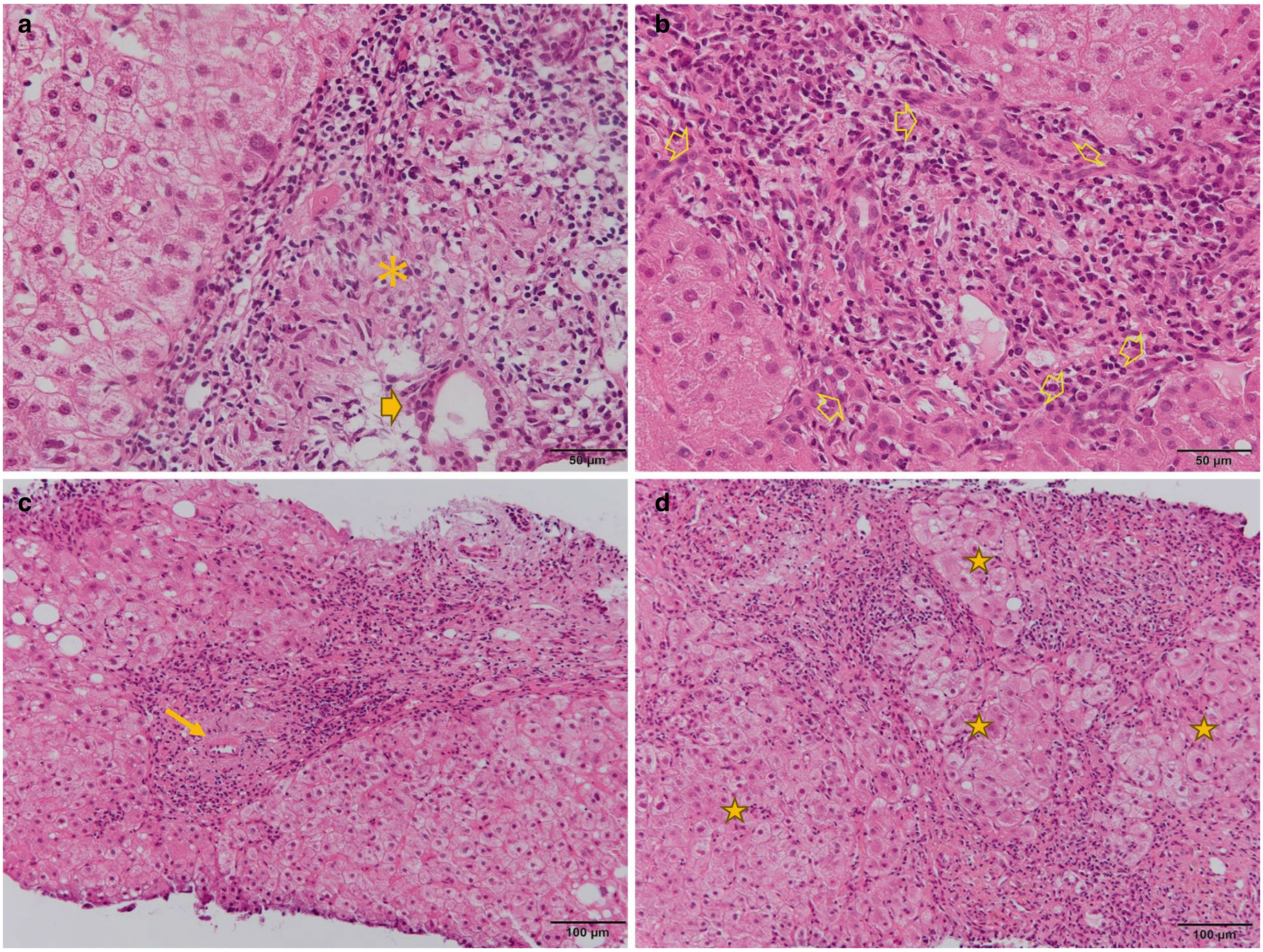

Fig. 60.1 Histological stages of PBC. Hematoxylin and eosin staining of liver sections from patients with PBC with characteristic features of (**a**) stage 1 PBC with the presence of epithelioid granuloma (*), damaged bile ducts (arrow) and lymphoma-plasmacytic infiltration; (**b**) stage 2 PBC with chronic inflammation and ductular proliferation(arrows), the margins of the portal tract are obscured by fibrosis and interface hepatitis; (**c**) stage 3 PBC showing broad fibrous septa, bridging fibrosis and ductopenia. Note that interlobular bile duct, which should be located adjacent to hepatic artery branch (long arrow), is missing and (**d**) stage 4 PBC showing fibrosis septa extending from the portal tracts. Regenerative nodules (stars) surrounding fibrous septa, liver cirrhosis and loss of interlobular bile ducts

Inquiry of the past use of medications contribute to differentiate drug-induced cholestasis. Of the multiple drugs that cause drug-induced cholestasis, phenothiazines, synthetic androgenic steroids, trimethoprim-sulfamethoxazole, diclofenac, oxacillin and ampicillin are the most common drugs associated with cholestasis. Gallstones or malignancy and PSC can be ruled out by biliary imaging, such as a right upper quadrant ultrasound, MRCP, ERCR, etc. Infectious diseases including bacterial, fungal and viral infections can be confirmed by laboratory testing. The absence of AMA, along with the patient's medical history, physical examination, laboratory examination and related imaging studies, can indicate other possible causes of cholestasis.

Therapy and Prevention

The symptoms of PBC, mainly fatigue and itch, greatly affect the quality of life. However, there are no standard recommended therapy to relieve fatigue. On the other hand, rifampicin, opiate antagonists and a number of anion-exchange resins such as cholestyramine and colestipol have been used in treating itchiness with variable effects in patients with PBC.

The primary objective of PBC treatment is to prevent disease progression and the development of cirrhosis and liver failure. Agents targeting immune-mediated pathogenesis and anti-inflammatory are probably most effective in the early stage of PBC, while anti-cholestatic and anti-fibrotic therapies are emphasized in the late stage of disease, which is characterized by fibrosis and cirrhosis development. Although UDCA and OCA are approved by the Food and Drug Administration (FDA) as first and second line of therapy respectively, cirrhotic patients hardly benefit and some PBC patients are non-responsive [13, 14]. UDCA is recommended as the standard first line treatment for PBC. The recommendation highlights a dose–response relationship and the importance of the 13–15 mg/kg dose [15]. UDCA is a endogenous bile acid, which plays its therapeutic role by multi-aspect mechanisms, including accelerating bile acid enterohepatic circulation, stabilizing the biliary HCO_3^- umbrella, anti-apoptosis and anti-inflammatory [16]. A large multicenter study indicated that UDCA therapy improved liver transplant (LT)-free survival in all patients with PBC, regardless of the disease stage and the observed biochemical response [15, 17]. Unfortunately, although UDCA monotherapy improved overall LT-free survival, approximately 30–40% patients do not respond favorably to UDCA. A recent study showed that PBC patients benefited more from add-on therapies in which UDCA is combined with glucocorticoids or immunosuppressants [18]. Bezafibrate combination with UDCA resulted in better biochemical response and lower predicted mortality or LT need than those treated with UDCA alone [19].

Finally, advances in the understanding on the immunological and cellular mechanisms of pathogenesis in PBC have opened up opportunities in mechanism-based target therapies for PBC and potential therapeutic strategies to improve the efficacy of existing treatments [20] (Table 60.3).

Table 60.3 Mechanism-targeted therapies in PBC

Targeting immunological mechanisms	B cells and related cytokines
	T cells and related cytokines
	Other immune cells and related immune signals
	Immune mediators and related signaling pathway
Targeting cellular mechanisms	Bile acid metabolism
	Bile acid receptor
	Farnesoid X receptor
	Peroxisome proliferator-activated receptor agonists
	Pregnane X receptor
	Apical sodium-dependent bile acid transporter (ASBT) inhibitors
Targeting liver fibrosis	NADPH oxidase 1 and 4
Emerging strategies	Targeting gut–liver axis and gut microbes
	Mesenchymal stem cells therapy
	Nanoparticles-mediated therapy

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Primary Sclerosing Cholangitis

61

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Abstract

Primary sclerosing cholangitis (PSC) is a male-predominant autoimmune-mediated inflammatory disease of the liver that affects both the large and small bile ducts that eventually progresses to cirrhosis, portal hypertension, and liver failure. PSC patients are usually asymptomatic at an early stage. About 80% of PSC patients also developed inflammatory bowel disease (IBD)—a majority of them have ulcerative colitis. Other PSC-IBD patients may have Crohn's disease. The accurate diagnosis of PSC is based on clinical history, liver biochemistry, and imaging with magnetic resonance imaging with cholangiopathy (MRI/MRCP) and endoscopic retrograde cholangiopancreatography (ERCP). A liver biopsy is performed when imaging results are indeterminate. A liver biopsy helps to differentiate small duct PSC from overlapping autoimmune hepatitis or IgG4 cholangiopathy. Although perinuclear antineutrophilic cytoplasmic antibodies, anti-nuclear antibodies, anti-muscle antibodies, and IgG4 may be detected, there are no disease-specific autoantibodies in PSC. PSC patients have a higher risk of developing cholangiocarcinoma, and cholangiocarcinoma surveillance is recommended. Since there is no effective cure for PSC, current treatments are directed at alleviating symptoms and improving quality of life. A liver transplant is necessary for advanced-stage PSC patients. Colon cancer prevention with an annual colonoscopy is recommended for PSC-IBD patients.

Keywords

Bile ducts · Inflammatory bowel disease · Ulcerative colitis · Crohn's disease · Imaging · Liver biopsy · Liver transplant · Cholangiocarcinoma

Description of Disease

Primary sclerosing cholangitis (PSC) is a male-predominant autoimmune-mediated inflammatory and fibrotic disease of the liver. The disease can manifest as intrahepatic small duct disease (SD-PSC), the classic PSC affecting both small and large ducts, or be associated with autoimmune hepatitis (AIH). Most patients are asymptomatic and remain undetected in the early stages.

However, persistent immune-mediated destruction of the biliary tree over time will lead to multifocal bile duct strictures. Biliary obstruction from strictures and recurrent bacterial bile duct infections cause chronic cholestatic liver damage that eventually progresses to liver cirrhosis, portal hypertension, and liver failure. The exact etiology of PSC is unclear. Genetic predisposition, environmental triggers, microbial dysbiosis, bacterial translocation in a defective intestinal mucosa, and abnormal autoimmune responses are likely involved. T-cell cytokine-mediated immune activation causes peribiliary myelofibrosis and destruction of the bile ducts [1–3].

PSC is a rare disease that affects 16.2/100,000 persons in the USA, with similar incidence in Caucasians and African Americans. The mean age of diagnosis is between 30 and 40 years. Close to 95% have pancolitis. Rectal sparing is

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more common in PSC-UC patients than in patients without PSC. Most Crohn's disease (CD) patients with PSC have colonic disease. Isolated ileitis, fistulizing, and fibro stenotic disease are very rare. The strong association with inflammatory bowel disease (PSD-IBD) may suggest that IBD could drive the aberrant immune responses in PSC. On the other hand, less than 5% of IBD patients have PSC. PSC-UC at 2.47% is more common than PSC-CD at 0.96% [4]. PSC can also be associated with other autoimmune diseases such as thyroiditis, type 1 diabetes mellitus, and rheumatoid arthritis. It can present as overlap syndromes with autoimmune hepatitis (PSC-AIH) [5].

PSC patients have increased risks of developing cholangiocarcinoma (HR 28.46), hepatocellular carcinoma (HR 21), gallbladder cancer (HR 9.19), pancreatic cancer (HR 5.26), and especially a 10–40-fold increase in colon cancer risk in PSC-IBD individuals [3]. There is no effective medical cure. Liver transplantation is the only treatment. The median survival rate for a liver transplant is 15–20 years from the initial diagnosis.

Signs and Symptoms

Most PSC patients are asymptomatic at an early stage. About 22% develop symptoms within 5 years of diagnosis. Upon progression of cholestatic liver disease, fatigue and pruritis are common with weight loss at more advanced stages. Intermittent right upper quadrant pain and pruritis are most frequent and can resolve spontaneously. Jaundice, abdominal pain, and fever can reflect existing ascending bacterial cholangitis (Table 61.1). Patients with progressive disease may show portal hypertension of hepatomegaly, splenomegaly, spider angiomas, and ascites [6].

Table 61.1 Symptoms of primary sclerosing cholangitis and their percentages [7]

Primary sclerosing cholangitis	
Symptoms	Frequency (%)
None	15–55
Fatigue	50–75
Pruritus	40–70
Jaundice	9–69
Abdominal pain	16–60
Weight loss	10–34
Fevers and chills	5–28
Hyperpigmentation	25

Laboratory Tests and Serology

Patients with unexplained abnormal cholestatic liver function tests should be investigated for PSC (Table 61.2). An increased serum alkaline phosphatase level that persists for more than 6 months, followed by a high-quality cholangiography showing focal strictures and saccular dilatation of the bile ducts, confirms the diagnosis of PSC. A liver biopsy is usually unnecessary unless the MRCP is normal or indeterminate. A liver biopsy helps determine small duct PSC (SD-PSC), overlapping autoimmune hepatitis (AIH), or IgG4 cholangiopathy.

A persistently elevated alkaline phosphatase (ALP) level is a hallmark of PSC. In some patients, serum aspartate and alanine aminotransferase levels are only mildly to moderately increased. The levels of ALP and bilirubin can fluctuate during the relapsing nature of cholestasis. Some IBD patients may have normal ALP. γ-Glutamyltransferase (GGT) was the only independent factor predicting the diagnosis of PSC (odds ratio, 1.8; 95% CI, 1.3–2.5) during the early disease stage. Elevated serum alkaline phosphatase, total bilirubin, aminotransferases, and GGT are seen in advanced cholestatic liver disease [8].

There are no antigen-specific autoantibodies in PSC. Although perinuclear antineutrophil cytoplasmic anti-

Table 61.2 Liver biochemistry indicative of PSC

Serological test				
	Normal range	Early stage	During the course	Advanced stage
Total bilirubin	0.3–1.2 mg/dL	Normal	Normal or fluctuate	+++
Alkaline phosphatase	36–92 U/L	++	++	+++
Aminotransferase, alanine (ALT)	0–35 U/L	Normal	+	++
Aminotransferase, aspartate (AST)	0–35 U/L	Normal	+	++
γ-Glutamyltransferase (GGT)	0–30 U/L	+	++	+++
Albumin	3.5–5.5 g/dL	Normal	–	– –

Key: + mild elevation; ++ moderate elevation; +++ high elevation; – mild decrease; -- moderate decrease

Table 61.3 Serological autoantibody detection

Serological tests [9, 10]		
Autoantibodies	Frequency	Remarks
Perinuclear antineutrophil cytoplasmic antibody (p-ANCA)	80%	Non-specific
Antinuclear antibodies (ANA)	20–60%	Non-specific
Anti-smooth muscle antibodies (ASM)	20–60%	Non-specific
Anti-mitochondrial antibodies (AMA)	Rare	Non-specific
IgG4	15%	Level usually <5.6 g/L
IgG4/IgG1 ratio <1 (serum IgG4 at level 1.4–2.8 g/L)		Exclude IgG4 sclerosing cholangitis

bodies (p-ANCA), anti-nuclear antibodies (ANA), and anti-smooth muscle antibodies can be detected in PSC patients, they are not disease-specific (Table 61.3).

Diagnostic Criteria

Patients with abnormal liver enzymes with persistent elevation of ALP should be investigated for liver diseases. A persistent elevation of serum alkaline phosphatase together with positive MRCP features will make the diagnosis of PSC possible without the need for a liver biopsy.

Imaging

Magnetic Resonance Imaging with Cholangiography

Magnetic resonance imaging with cholangiography (MRI/MRCP) uses MRI to generate detailed images of the hepatobiliary and pancreatic systems. It is non-invasive and non-radioactive and can define multifocal strictures and segmental biliary dilatation better than a CT scan or ultrasound.

Considering safety, MRCP is preferable to endoscopic retrograde cholangiopancreatography (ERCP) as it requires no sedation, does not induce post-ERCP pancreatitis, and does not contaminate the biliary tree. It can highlight the entire upstream ductal system with a high-grade stricture, even when ERCP fails to opacify the ducts. ERCP is no longer used solely as a diagnostic test but for its therapeutic capabilities in biliary drainage, tissue sampling, dilation, and stenting [11].

A high-resolution 3D MRCP with maximal intensity projections can accurately detect small intrahepatic and dominant strictures. A contrast-enhanced MRI can highlight features of progressive disease such as biliary ductal strictures, biliary ductal dilatations, ductal wall thickening, atrophy, or enlargement of liver lobes (Fig. 61.1).

A 3D MRCP with maximal intensity projections showed the intrahepatic biliary system in the same patient as shown in (Fig. 61.2).

Endoscopic Retrograde Cholangiopancreatography (ERCP)

For classic primary sclerosing cholangitis (PSC), ERCP provides higher-resolution images than MRCP. The ERCP criterion for a dominant stricture in the common bile duct is ≤1.5 mm in diameter and in the hepatic duct is ≤1 mm. A high-grade stricture is defined as a >75% reduction in the common bile duct or hepatic ducts on MRCP. A relevant stricture signifies a biliary stricture associated with signs or symptoms of obstructive cholestasis and bacterial cholangitis (Table 61.4).

Small duct-primary sclerosing cholangitis (SD-PSC) involves ducts less than 400 nm in size. They are below the resolution of high-definition cholangiography. The radiographical findings in SD-PSC are non-specific. MRI features showing inhomogeneous liver enhancement, heterogeneous parenchymal signal intensity, periductal enhancement, gallbladder dilatation, and periportal lymphadenopathy do not confirm PSC [14].

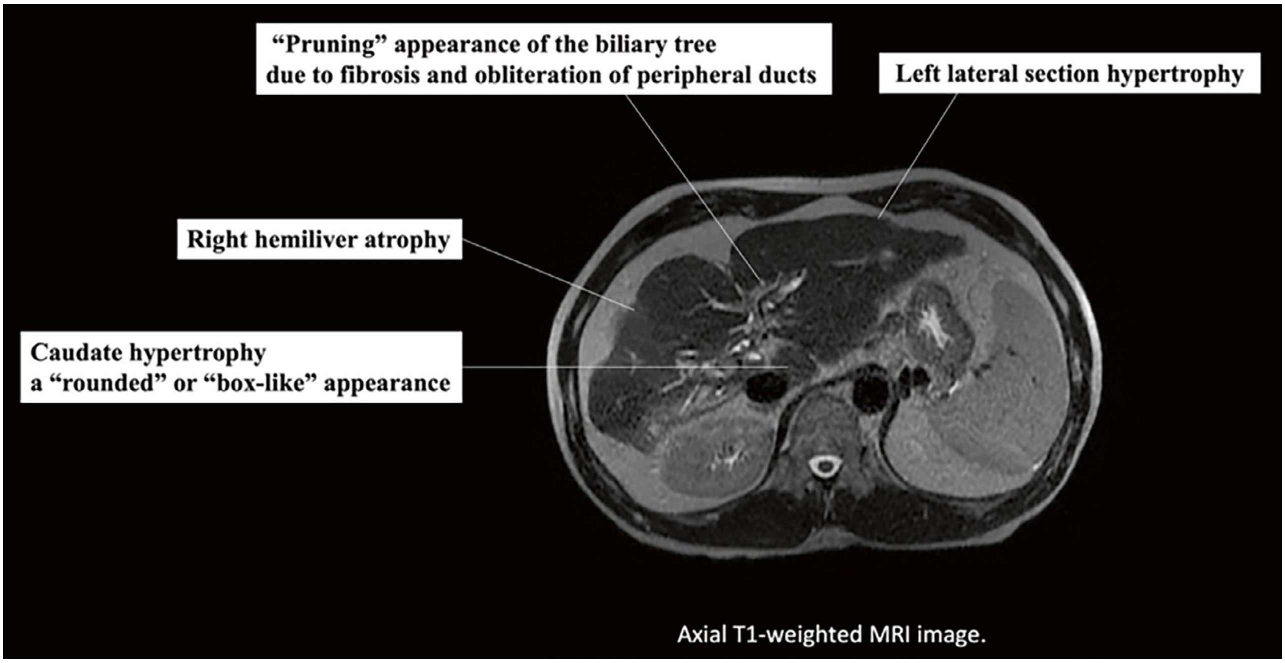
"Pruning" appearance of the biliary tree
due to fibrosis and obliteration of peripheral ducts
Left lateral section hypertrophy
Right hemiliver atrophy
Caudate hypertrophy
a "rounded" or "box-like" appearance
Axial T1-weighted MRI image.

Fig. 61.1 MRI showing classic features of advanced primary sclerosing cholangitis in a 52-year-old man initially presented with pruritis and raised ALP >1000

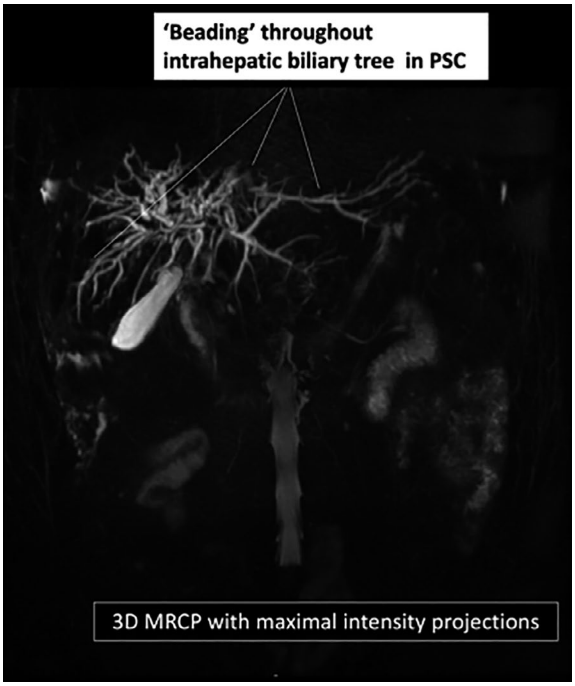
'Beading' throughout
intrahepatic biliary tree in PSC
3D MRCP with maximal intensity projections

Fig. 61.2 3D MRCP with maximal intensity projections

Liver Biopsy

A liver biopsy is performed when the MRI/MRCP is indeterminate. The histopathological features help to diagnose small duct-PSC (SD-PSC), overlapping autoimmune hepatitis (AIH), and IgG4 cholangiopathy. Autoimmune hepatitis overlap shows features of lymphoplasmacytic interface hepatitis, and the diagnosis is confirmed by serology as shown in Table 61.5. IgG4 is present in both PSCs but more specifically for IgG4 cholangiopathy [15].

In addition to its value in defining SD-PSC and AIH overlap or IgG4 cholangiopathy, the histopathological features can help stage the severity of the disease [16].

Table 61.4 MRI/MRCP and ERCP imaging features in various stages of PSC [12, 13]

PSC	Features	Remarks
Early progressive disease	"Beading" of intrahepatic ducts can result from multifocal strictures intervening with relatively normal segments on cholangiography	
	Combined intra- and extrahepatic ducts	Most common
	Intrahepatic duct alone	15–25%
	Extrahepatic ducts alone	5–10%
Advanced disease	Ductal wall thickening	
	"Pruning" of the bile ducts is due to fibrosis and obliteration of more peripheral intrahepatic ducts	
Biliary cirrhosis	"Rounded" or "Box-like" appearance from caudate hypertrophy, left lateral section hypertrophy, and right hemiliver atrophy	

Stage 1: Cholangitis or portal hepatitis
Stage 2: Periportal fibrosis or periportal hepatitis
Stage 3: Septal fibrosis, bridging necrosis, or both
Stage 4: Biliary cirrhosis

In summary, the accurate diagnosis of PSC involves a detailed process from clinical history, laboratory test, imaging, and even biopsy when needed (Fig. 61.3).

Table 61.5 Histopathological and serological features in differential diagnosis of PSC

Diagnostic histopathological features		
PSC	Overlap autoimmune hepatitis (AIH)	IgG4 cholangiopathy
Periductal fibrosis—the classic "onion ring" appearance is not always present	Lymphoplasmacytic interface hepatitis	IgG4-positive plasma cells in tissue
Fibro-obliterative duct lesions		
Ductular proliferation includes bile duct loss, ductular reaction		
Cholestasis in periportal hepatocytes		

Diagnostic serological tests		
PSC (non-specific)	Overlap autoimmune hepatitis (AIH)	IgG4 cholangiopathy
Perinuclear antineutrophil cytoplasmic antibody (p-ANCA)	Antinuclear antibodies (ANA) **AIH type 1 or 2**	IgG4
Antinuclear antibodies (ANA)	Smooth muscle antibodies (SMA) **AIH type 1**	
Anti-smooth muscle antibodies (ASM)		
Anti-mitochondrial antibodies (AMA)	Anti-liver kidney microsome type1 (LKM1) **AIH type 2**	
IgG4	Anti-liver cytosol 1 (anti-LC1) **AIH type 2**	
	Anti-soluble liver antibody (anti-SLA)	

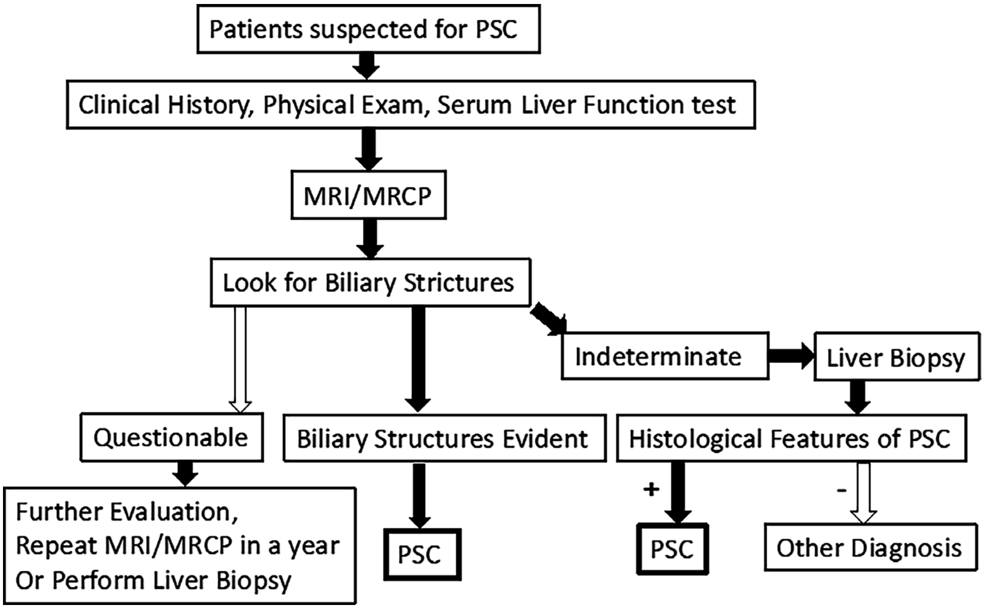
Patients suspected for PSC
Clinical History, Physical Exam, Serum Liver Function test
MRI/MRCP
Look for Biliary Strictures
Indeterminate
Liver Biopsy
Questionable
Biliary Structures Evident
Histological Features of PSC
+
-
Further Evaluation,
Repeat MRI/MRCP in a year
Or Perform Liver Biopsy
PSC
PSC
Other Diagnosis

Fig. 61.3 Diagnostic algorithm for primary sclerosing cholangitis. (Adopted and modified from AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. Hepatology 2023;77(2)659–702)

Cholangiocarcinoma (CCA) in PSC Patients

The risk of cholangiocarcinoma is several hundred-fold higher in PSC patients. The annual incidence of CCA is 0.6–1.5%. The cumulative incidence of CCA increases over time but does not directly correlate with the duration of the disease. The incidence rate is 6–11% after 10 years and 20% after 30 years. Surveillance of asymptomatic patients with US or MRI/MRCP with CA19-9 is suggested every 6–12 months. A directed evaluation of the biliary tree with ERCP, choledochoscopy, or endoscopic ultrasound for CCA is initiated for focal, eccentric, and nodular thickening of a dominant stricture and/or increasing CA19-9 [17]. In a study by Eaton et al. [18], the sensitivity of cholangiocarcinoma detection is close to 90% by combining typical and possible MRI imaging features of CCA using the following criteria:

Definition of MRI Features

Definite/typical CCA includes the following:

1. A perihilar mass (with or without intrahepatic or intraductal mass lesions) with progressive enhancement on delayed phase imaging
2. A malignant stricture (periductal focal soft tissue thickening with vascular narrowing or encasement or periductal focal soft tissue thickening that enhances delayed phase imaging)

Possible CCA includes the following:

1. Stricture with non-focal periductal thickening but without delayed phase enhancement or vascular narrowing (or encasement)
2. Progressive lobar atrophy secondary to worsening perihilar stricture
3. Ill-defined, irregular, delayed enhancement of ductal wall without distinct mass

Therapy and Prevention

Due to the complex pathogenetic mechanisms that involve microbial interactions and aberrant immune response leading to progressive biliary fibrosis, there is no effective cure for PSC. Medical therapy that can significantly alter the natural history of PSC remains a clinical challenge. Liver transplantation remains the only curative therapy. Current approaches are directed at alleviating symptoms and improving the quality of life [2].

Treating Pruritis

Effective pharmacotherapeutic agents in treating cholestatic pruritis include bile acids sequestrants, antihistamines, m-opioid antagonists, and selective serotonin reuptake inhibitors (SSRIs), pregnane X receptor (PXR) agonists, and peroxisome proliferator-activated receptor (PPAR) agonists.

Improving Biochemistry

Ursodeoxycholic acid (UDCA) is commonly used in cholestatic liver disease, including primary biliary cholangitis. A low dose, 15–20 mg/kg daily, improves ALP level but does not provide histological improvements or impact survival. A high dose of 28–30 mg/kg daily is not recommended because of severe adverse effects [19].

Immunosuppressive Therapies

Immunosuppressive drugs are effective in treating overlap AIH-PSC and IgG4 disease but not in PSC alone.

Anti-fibrotic Therapies

Anti-fibrotic agent lysyl oxidase-like (LOXL)-2 inhibitors are ineffective, while anti-integrin and nonsteroidal farnesoid X receptor (FXR) agonists showed beneficial effects in preliminary trials [2].

Relieving Biliary Obstruction

Endoscopic dilation and stenting are effective in relieving biliary obstruction and treating cholangitis.

Modulating the Gut Microbiome

In small studies, oral vancomycin improved liver tests and Mayo risk score. The concept of modulating gut microbiome by fecal microbiota transplantation is under investigation.

Cancer Surveillance

Colon cancer prevention with an annual colonoscopy is recommended for PSC-IBD patients. Cholangiocarcinoma surveillance using MRI/MRCP, liver and gallbladder cancer are monitored by ultrasonography every 6 months [20].

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Autoimmune Pancreatitis

62

Guillem Soy and Eva C. Vaquero

Abstract

Autoimmune pancreatitis (AIP) is a particular form of immune-mediated inflammatory disease of the pancreas characterized by histological features of lymphoplasmacytic infiltrate and fibrosis and excellent response to corticosteroid therapy. AIP is considered a rare entity, and it is generally presented with obstructive jaundice associated with an inflammatory pancreatic mass or an inflammatory stricture of the bile duct. There are two types of AIP, which differ in their epidemiology, pathological features, and clinical manifestations. Type 1 AIP is part of the IgG4-related systemic disease, whereas type 2 AIP is a specific pancreatic disorder. AIP diagnosis is challenging, especially because its clinical and radiological manifestations can mimic pancreatic and biliary cancer, which often leads to unnecessary pancreatic surgery, but it can also contribute to delayed diagnosis of biliopancreatic malignancy. AIP diagnosis is based on a consensus of clinical, serological, imaging, and pathologic criteria as well as response to corticosteroids.

Keywords

Autoimmune pancreatitis · IgG4-related systemic disease · Type 1 autoimmune pancreatitis · Type 2 autoimmune pancreatitis · Lymphoplasmacytic sclerosing pancreatitis · Idiopathic duct-centric pancreatitis

Introduction

Autoimmune pancreatitis (AIP) is an immune-mediated fibro-inflammatory benign disease of the pancreas that, although first cases were described in the early 60s, it was not conceptualized and definitively named as AIP until 1995 by Yoshida et al. [1]. The International Association of Pancreatology (IAP) defined AIP as a distinct form of pancreatitis that often presents with obstructive jaundice with or without a pancreatic mass, with characteristic histological changes that include lymphoplasmacytic infiltration and fibrosis of the pancreatic gland and display an excellent response to corticosteroids [2].

AIP is a rare entity, with a prevalence of 10.1 cases per 100,000 inhabitants and an incidence of 3.1 cases per 100,000 inhabitants in Japan [3]. Although there is no robust epidemiological data from Western populations, a German single-center study suggests that the incidence of AIP in Europe might be lower than in Asia (0.29 cases per 100,000 inhabitants) [4].

AIP has been divided into two distinct types: type 1 and type 2 AIP [2, 5] (see Table 62.1). Both entities share common histopathologic features (periductal lymphoplasmacytic infiltrate and periductal fibrosis), might have a similar clinical presentation (obstructive jaundice with/without pancreatic mass), and have a great response to corticosteroids [2, 5, 6]. However, they differ significantly regarding demographics, serology, other organ involvement, and disease relapse [2, 5]. Furthermore, there are unique histopathologic features specific to each type [6].

Type 1 AIP is more frequent in Asia; it is predominant in male subjects (3:1), and the mean age at diagnosis is around the sixth decade of life [7]. Type 1 AIP (also known as IgG4-related pancreatitis) is considered the pancreatic manifestation of IgG4-related systemic disease, characterized by serum elevation of IgG4 levels and other organ involvement due to abundant infiltration of IgG4-positive plasma cells (i.e., common bile duct and proximal biliary tree, gallbladder, salivary glands, lacrimal glands, retroperitoneum, kid-

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Table 62.1 Main differences between type 1 AIP vs. type 2 AIP

Features	Type 1 AIP	Type 2 AIP
Clinical features		
Age of presentation	60th decade	40–50th decade
Sex	Male > female (3:1)	No sex bias
Geographical location	Asia > Europe & USA	Europe & USA > Asia
Common clinical presentation	Painless obstructive jaundice	Painless obstructive jaundice, single/recurrent AP
Other organ involvement	IgG4-related systemic disease (gallbladder, biliary tree, lacrimal gland, salivary glands, retroperitoneum, kidney)	None. Frequently associated with IBD (particularly with ulcerative colitis)
Serum IgG4 level	Elevated	Normal
Steroid responsiveness	Excellent	Excellent
Recurrence after steroid withdrawal	Common	Uncommon
Pathologic features		
Histopathologic hallmark	LPSP: (1) dense infiltration of plasma cells and lymphocytes, (2) storiform fibrosis, (3) obliterative phlebitis, (4) abundant IgG4 plasma cells	IDCP. GELs. Absence or scarce infiltrate of IgG4 plasma cells
Periductal lymphoplasmacytic infiltrate	Common	Common
Inflammatory cellular stroma	Common	Common
Storiform fibrosis	Prominent	Uncommon
Obliterative phlebitis	Frequent	Uncommon
Lymphoid follicles	Prominent	Uncommon
IgG4-positive plasma cell infiltrate	Marked (>10/HPF)	Less prominent (<10/HPF) or absent
Granulocytic epithelial lesions	Absent	Frequent and pathognomonic
Acinar neutrophilic infiltrate	Absent	Very common and pathognomonic

AP acute pancreatitis, *GEL* granulocyte epithelial lesion, *HPF* high-power field, *IBD* inflammatory bowel disease, *IDCP* idiopathic duct-centric pancreatitis, *LPSP* lymphoplasmacytic sclerosing pancreatitis
Adapted from [2, 5]

ney) [7, 8]. The histopathologic description of type 1 AIP is lymphoplasmacytic sclerosing pancreatitis (LPSP) or AIP without granulocyte epithelial lesions (GELs) [2, 5, 6]. Even though pancreatic and extrapancreatic manifestations respond to steroid therapy, recurrence after withdrawal is frequent, particularly when extrapancreatic involvement is present [2, 5, 7, 8].

Type 2 AIP is more commonly reported in Europe (13%) and the USA (14%) than in Asia (4%) [9]; patients are generally younger at diagnosis, and gender bias is not present [2, 5, 7]. Type 2 AIP is a specific pancreatic disorder unrelated to IgG4-related systemic disease; thus, serum IgG4 is not elevated, and it does not present other organ involvement [2, 5, 7]. Inflammatory bowel disease (IBD) has a high prevalence in AIP patients (10–17% in Europe), particularly in type 2 AIP (79%) compared to type 1 AIP (21%), being ulcerative colitis much more prevalent than Crohn's disease (75% vs. 25%) [10]. Histopathologic description is idiopathic duct-centric pancreatitis (IDCP) or AIP with GELs [2, 5, 6]. Compared to type 1 AIP, recurrence after steroid withdrawal is rare in type 2 AIP (relapse rate 31% in type 1 AIP vs. 8% in type 2 AIP) [2, 5, 7, 9]. Given that type 2 AIP lacks serum biomarkers and other organ involvement, definitive diagnosis requires pancreatic histological confirmation (see section "Diagnostic Criteria"), which is not frequently available. This could explain why type 2 AIP is less frequently reported than type 1 AIP [2].

Diagnosis

Clinical Manifestations

The most frequent clinical presentation of type 1 AIP is painless obstructive jaundice (60%) either due to an inflammatory pancreatic mass or to an inflammatory stenosis of the common bile duct. It may also present as abdominal pain or acute pancreatitis (single or recurrent episodes) [2, 11]. In type 2 AIP, most patients present with acute pancreatitis (60%) followed by painless jaundice (30%) [11, 12]. During follow-up, features of painless chronic pancreatitis with pancreatic atrophy, calcifications, and both exocrine and endocrine pancreatic insufficiency might appear. However, marked cachexia, inability to eat, and opioid-requiring pain are more suggestive of pancreatic cancer, which is the most important differential diagnosis to be made [2].

Serology

Serum IgG4 elevation is the single best biomarker of type 1 AIP. However, it is only present in around 60% of cases [2, 7, 8]. Furthermore, false-positive results might also occur in the setting of pancreatic cancer, chronic pancreatitis, and other extrapancreatic diseases; thus, the sole elevation of this biomarker is not sufficient for AIP diagnosis [2]. IgG4 elevation achieves reasonable specificity when serum levels are beyond 2 times the upper limit of normal (ULN) and is strongly suggestive of type 1 AIP if other features of the disease are present (see section "Diagnostic Criteria") [2]. Regarding type 2 AIP, serum IgG4 concentration is within the normal range; thus, it has no diagnostic value [2, 7, 8]. AIP might also be associated with hypergammaglobulinemia, total IgG elevation, serum IgE elevation, hypereosinophilia, or the presence of anti-nuclear antibodies, but none of them achieves sufficient diagnostic yield to be considered as diagnostic markers.

Radiological Imaging

Imaging studies are the first step for diagnosing suspected AIP. Typical features of AIP in cross-sectional imaging consist of a diffuse enlarged and swollen pancreas ("sausage-like" shape) with an edematous capsule-like rim outlining the gland and stenosis of the main pancreatic duct without upstream dilatation or cutoff [2, 8]. However, almost 75% of patients present with a radiological focal enlargement of the pancreas which might be misdiagnosed as pancreatic malignancy [11]. Features that would suggest pancreatic cancer are the presence of a low-density pancreatic mass with cutoff and upstream dilatation (>5 mm) of the main pancreatic duct and pancreatic atrophy [2].

Other Organ Involvement

Most of the patients with type 1 AIP (around 40–80%) present other organ involvement as part of the IgG4-related systemic disease [2, 7, 11]. These extrapancreatic manifestations might precede AIP, occur simultaneously, or develop after it, and they respond to corticosteroid therapy as well [8]. Other organ involvement may be diagnosed by histological evaluation of the affected organ (dense lymphoplasmacytic infiltration with IgG4-positive plasma, storiform fibrosis, obliterative phlebitis), imaging (extrapancreatic bile duct stricture, retroperitoneal fibrosis, pseudotumor of the organ affected), or clinical examination (e.g., salivary gland enlargement) [2]. The most frequent extrapancreatic manifestation of IgG4-related systemic disease involves the common bile duct and biliary tree (immune-related cholangitis or IgG4-related sclerosing cholangitis) [8]. Other frequently affected organs are the gallbladder, retroperitoneum, salivary glands, lacrimal glands, and kidneys. Type 2 AIP is a specific pancreatic disorder without any extrapancreatic involvement [2, 5, 7]. However, IBD is particularly prevalent in type 2 AIP, especially ulcerative colitis [10].

Histology

AIP displays certain histopathologic features which are different from other types of pancreatitis [5]. Some of these characteristics are found in both type 1 and type 2 AIP (periductal lymphoplasmacytic infiltration and a diffuse or patchy inflammatory cellular stroma with abundant lymphocytes, plasma cells, and eosinophils), while other findings are exclusive for one specific type, which helps to differentiate one from the other [5, 6] (see Table 62.1).

Type 1 AIP or LPSP (AIP without GELs) has the following essential histological features: (1) lymphoplasmacytic infiltration surrounding small and medium-size pancreatic ducts without lumen destruction (absent granulocyte infiltration), (2) storiform fibrosis (swirling or spiraling fibrosis localized around ducts and veins and infiltrated by a dense lymphoplasmacytic component), (3) obliterative phlebitis (lymphoplasmacytic infiltrate surrounding pancreatic veins which obliterates vascular lumen), and (4) abundant IgG4-positive plasma cells [5, 6].

As type 1 AIP, type 2 AIP or IDCP (AIP with GELs) also presents periductal lymphoplasmacytic infiltration which might extend in a diffusely or patchy manner to the pancreatic parenchyma leading to inflammatory cellular stroma and fibrosis. Type 2 AIP might also present storiform fibrosis and obliterative phlebitis, although they are much less prominent than type 1 AIP. The most characteristic histopathological features of type 2 AIP are as follows: (1) the presence of neutrophilic infiltrates known as GELs affecting small and medium-size pancreatic ducts (which may lead to lumen destruction and obliteration) and potentially extending to the pancreatic parenchyma causing acini destruction and (2) the scanty or complete absence of IgG4-positive plasma cells in the pancreatic specimen [5, 6].

Diagnostic Criteria

Due to the difficulty in diagnosing AIP and differentiating it from other pancreatic diseases, several diagnostic criteria, such as the Japanese Pancreatic Society criteria [13] or the American HISORt criteria from the Mayo Clinic [14], had been proposed in the past. In 2011, the International Association of Pancreatology (IAP) published the International Consensus Diagnostic Criteria (ICDC) for AIP with the intention to have universally accepted criteria to be applied worldwide [2]. The ICDC was developed after an extensive review of previous existing criteria, and they take into consideration clinical practice differences within multiple countries. These criteria include five cardinal features for diagnosis: (1) pancreatic parenchymal and ductal morphology at imaging, (2) serum IgG4 levels, (3) other organ involvement, (4) pancreatic histology (procured by surgical specimen or pancreatic biopsy), and (5) glucocorticoid responsiveness. Each feature is divided into levels 1 or 2 according to the diagnostic reliability [2] (see Tables 62.2 and 62.3). After applying these criteria, a definite or probable diagnosis of type 1 AIP or type 2 AIP can be established (see Table 62.4). It is important to highlight that type 1 AIP can be diagnosed without pancreatic histology. However, given that type 2 AIP lacks reliable serum biomarkers and other organ involvement, definitive diagnosis requires histological confirmation of neutrophilic injury to the pancreatic ducts on surgical specimens, which is not frequently available. This could explain why type 2 AIP is less frequently reported than type 1 AIP [2]. In some cases, distinguishing between type 1 and type 2 AIP may not be possible (AIP type not otherwise

Table 62.2 Level 1 and level 2 criteria for type 1 AIP using ICDC criteria [2]

Criterion		Level 1	Level 2
P	Parenchymal changes	*Typical:* Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	*Indeterminate including atypical*[a]: Segmental/focal enlargement with delayed enhancement
D	Ductal imaging	Long stricture of the MPD (>1/3 length) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (MPD < 5 mm)
S	Serology	IgG4 ≥ 2× UPN	IgG4, 1–2× UPN
OOI	Other organ involvement	A or B	A or B
		(A) Histology of extrapancreatic organs. ≥3 of the following:	(A) Histology of extrapancreatic organs. Including endoscopic biopsies of bile duct[b]. Both of the following:
		(A1) Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration	(A1) Marked lymphoplasmacytic infiltration without granulocytic infiltration
		(A2) Storiform fibrosis	(A2) Abundant (>10 cells/HPF) IgG4-positive cells
		(A3) Obliterative phlebitis	
		(A4) Abundant (>10 cells/HPF) IgG4-positive cells	
		(B) Typical radiological evidence. Any of the following:	(B) Physical or radiological evidence. Any of the following:
		(B1) Proximal and distal bile duct stricture or segmental/multiple proximal (hilar/intrahepatic) bile duct stricture	(B1) Symmetrical enlarged salivary/lachrymal glands
		(B2) Retroperitoneal fibrosis	(B2) Radiological evidence of renal involvement described in association with AIP
H	Histology of the pancreas	LPSP (core biopsy or resection)	LPSP (core biopsy)
		At least 3/4 of the following:	Any two of the following:
		(1) Periductal lymphoplasmacytic infiltration without granulocytic infiltration	(1) Periductal lymphoplasmacytic infiltration without granulocytic infiltration
		(2) Storiform fibrosis	(2) Storiform fibrosis
		(3) Obliterative phlebitis	(3) Obliterative phlebitis
		(4) Abundant (>10 cells/HPF) IgG4-positive cells	(4) Abundant (>10 cells/HPF) IgG4-positive cells
Rt	Response to steroid[c]	Diagnostic steroid trial: Rapid (≤2 weeks) radiological improvement/resolution in pancreatic/extrapancreatic manifestations	

AIP autoimmune pancreatitis, *EUS FNA/FNB* endoscopic ultrasound-guided fine needle aspiration/fine needle biopsy, *HPF* high-power field, *ICDC* International Consensus Diagnostic Criteria, *LPSP* lymphoplasmacytic sclerosing pancreatitis, *MPD* main pancreatic duct, *UPN* upper limit of normal value

[a] Atypical: Some AIP cases show low-density mass, MPD dilatation, or retrograde parenchymal atrophy. Such features in patients with obstructive jaundice and/or pancreatic mass are highly suggestive of pancreatic cancer. Therefore, these patients should be managed as pancreatic cancer unless there is strong collateral evidence of AIP and a thorough workup for cancer is negative

[b] Endoscopic biopsies of duodenal papilla are a useful adjunctive method because the ampulla often is pathologically involved in AIP

[c] Diagnostic steroid trials should be conducted carefully by pancreatologists only after a negative workup for pancreatic cancer including EUS-FNA/FNB

Table 62.3 Level 1 and level 2 criteria for type 2 AIP using ICDC criteria [2]

Criterion		Level 1	Level 2
P	Parenchymal changes	*Typical*: Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	*Indeterminate including atypical*[a]: Segmental/focal enlargement with delayed enhancement
D	Ductal imaging	Long stricture of the MPD (>1/3 length) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (MPD <5 mm)
OOI	Other organ involvement	None	Clinically diagnosed IBD
H	Histology of the pancreas	IDCP	IDCP
		Both of the following	Both of the following
		(1) Granulocytic infiltration of duct wall (GEL) with or without granulocytic acinar inflammation	(1) Granulocytic and lymphoplasmacytic acinar infiltration
		(2) Absent or scant (0–10 cells/HPF) IgG4-positive cells	(2) Absent or scant (0–10 cells/HPF) IgG4-positive cells
Rt	Response to steroid[b]	Diagnostic steroid trial: Rapid (≤2 weeks) radiological improvement/resolution in pancreatic manifestations	

AIP autoimmune pancreatitis, *EUS FNA/FNB* endoscopic ultrasound-guided fine needle aspiration/fine needle biopsy, *GEL* granulocyte epithelial lesion, *HPF* high-power field, *IBD* inflammatory bowel disease, *ICDC* International Consensus Diagnostic Criteria, *IDCP* idiopathic duct-centric pancreatitis, *MPD* main pancreatic duct, *UPN* upper limit of normal value

[a] Atypical: Some AIP cases show low-density mass, MPD dilatation, or retrograde parenchymal atrophy. Such features in patients with obstructive jaundice and/or pancreatic mass are highly suggestive of pancreatic cancer. Therefore, these patients should be managed as pancreatic cancer unless there is strong collateral evidence of AIP and a thorough workup for cancer is negative

[b] Diagnostic steroid trial should be conducted carefully by pancreatologists only after negative workup for pancreatic cancer including EUS-FNA/FNB

Table 62.4 Diagnosis of definitive and probable AIP using ICDC criteria [2]

Diagnosis	Primary basis for diagnosis	Imaging evidence	Collateral evidence
AIP type 1			
Definitive type 1 AIP	Histology	Typical/indeterminate	Histologically confirmed LPSP (level 1H)
	Imaging	Typical	Any non-D level 1/level 2
		Indeterminate	≥2 from level 1 (+ level 2 D)
	Response to steroid	Indeterminate	Level 1 S/OOI + Rt or Level 1 D + level 2 S/OOI + Rt
Probable type 1 AIP		Indeterminate	Level 2 S/OOI + Rt
AIP type 2			
Definitive type 2 AIP		Typical/indeterminate	Histologically confirmed IDCP (level 1H) or diagnosis of IBD + level 2H + Rt
Probable type 2 AIP		Typical/indeterminate	Level 2H/diagnosis of IBD + Rt

AIP autoimmune pancreatitis, *D* ductal changes, *H* Histology, *IBD* inflammatory bowel disease, *ICDC* International Consensus Diagnostic Criteria, *IDCP* idiopathic duct-centric pancreatitis, *LPSP* lymphoplasmacytic sclerosing pancreatitis, *OOI* other organ involvement, *Rt* response to steroid, *S* serology

specified [NOS]), especially when imaging findings and steroid responsiveness support AIP but histology is unavailable, IgG4 plasma levels are normal, and other organ involvement is absent [2].

Differential Diagnosis

As previously mentioned, when considering AIP diagnosis, the most important aspect is to rule out pancreatic malignancy, which is more frequent than AIP. This is essential as AIP can be resolved with pharmacological treatment with an excellent prognosis, while the only curative strategy for pancreatic cancer is surgery, and it exhibits a worse prognosis. However, differentiating AIP from pancreatic cancer can be really challenging in certain situations, especially when AIP presents as a focal mass, or its diagnosis is not straightforward [2, 8]. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) or fine-needle biopsy (EUS-FNB) is recommended mostly to rule out pancreatic malignancy [2, 15]. Evidence regarding EUS-guided sampling for histological diagnosis of AIP on the other hand has been more controversial as its diagnostic yield can be compromised given the patchy distribution of the disease throughout the pancreas and the difficulty to acquire large core biopsies with preserved tissue architecture with EUS-FNA samples [8, 15]. However, recent evidence suggests that EUS-FNB (rather than EUS-FNA) and larger needles (19-gauge rather than standard 22-gauge) might have a better diagnostic yield and enable histological diagnosis in an important subset of patients [8, 15]. Indeed, a recent metanalysis reported a diagnostic yield of AIP of 87.2% for FNB and 55.8% for FNA [16]. If AIP is still suspected but not confirmed after EUS-guided sampling, a 2-week steroid trial with close reassessment of imaging and Ca 19.9 may be useful for differential diagnosis of AIP and pancreatic cancer given that steroid responsiveness is almost universal, which is why it is included in the ICDC for AIP [2, 17]. It is important to remember that a negative workup for malignancy including EUS-FNA/FNB is a prerequisite for steroid trial, based on current IAP guidelines [2, 18]. If there is poor or absent steroid responsiveness after a therapeutic trial based on cross-sectional imaging studies, revaluation of the diagnosis including reassessment of pancreatic cancer is mandatory [2, 17, 18]. We should keep in mind that a negative biopsy is not an absolute guarantee of nonmalignancy and repeating EUS-FNA is warranted in this scenario [15, 18]. Finally, although surgery is generally not indicated for patients with AIP, it might be considered when suspicion of pancreatic cancer cannot be excluded with absolute certainty after a complete diagnostic workup [8, 18].

Treatment

All symptomatic patients with pancreatic involvement (obstructive jaundice, abdominal pain) or symptomatic other organ involvement should be treated. For asymptomatic patients, treatment should be started in case of (1) persistent pancreatic mass with collateral evidence of AIP and negative workup of pancreatic cancer after EUS-FNA/FNB, (2) persistence of liver test abnormalities (cholestasis) in cases of associated IgG4-related sclerosing cholangitis, or (3) subclinical situations that could lead to irreversible organ failure [18].

First-line treatment for induction of remission is glucocorticoids (if there is no contraindication) [18], which achieve excellent remission rates (92–99%) [3, 9, 11]. The recommended treatment dosage for induction is prednisone 0.6–1.0 mg/kg/day (approximately 30–40 mg/day). Response to initial therapy should be assessed in 2–4 weeks using clinical, serological (liver enzymes and IgG4), and imaging markers (repeated cross-sectional imaging studies), in which a clear improvement (if not complete resolution) should be evident [18]. If there is a poor or absent response to glucocorticoids, revaluation of the diagnosis including pancreatic cancer is warranted [15, 18].

Considering that painless obstructive jaundice is the most frequent clinical presentation of AIP, endoscopic biliary stenting might be useful in some situations to prevent biliary infection and the use of brushing and cytology to differentiate IgG4-related sclerosing cholangitis and cholangiocarcinoma [18]. However, given the excellent and fast response to glucocorticoid therapy, obstructive jaundice in the context of definitive AIP and without evidence of biliary infection can be safely and effectively managed with corticosteroids alone without the need for biliary stenting under the supervision of experienced pancreatologists and with close monitoring. Furthermore, in case biliary stenting is needed, it can be safely removed once steroid responsiveness has been achieved [18, 19].

After response assessment, glucocorticoid dose should be maintained until 4–8 weeks since starting and then gradually tapered 5 mg every 2 weeks until complete withdrawal. Treatment tapering generally lasts 12 weeks [18]. Given that relapse rates in type 1 AIP are significantly higher than in type 2 AIP (around 40% vs. less than 10%) [9, 11], low doses of steroid maintenance therapy (2.5–7.5 mg/day) or immunomodulators such as azathioprine, methotrexate, or mycophenolate mofetil might be considered, especially in those cases with a higher risk of relapse (IgG4-related sclerosing cholangitis, multiorgan involvement [≥2], remarkably high serum IgG4 levels before treatment [IgG4 > ×4 ULN], delayed radiological response or persistent high serum IgG4 levels after treatment) [8, 18]. If relapse occurs, reintroduction of steroid therapy and addition of immunomodulators as steroid-sparing agents while tapering glucocorticoids might be an effective strategy. It is important to highlight that immunomodulators require overlap with steroids for 6–8 weeks, thus not being effective for induction therapy [18, 20]. Rituximab might be considered if patients are intolerant or resistant to high-dose glucocorticoids to achieve and maintain remission [20]. Figure 62.1 presents a treatment algorithm of AIP based on IAP consensus [18].

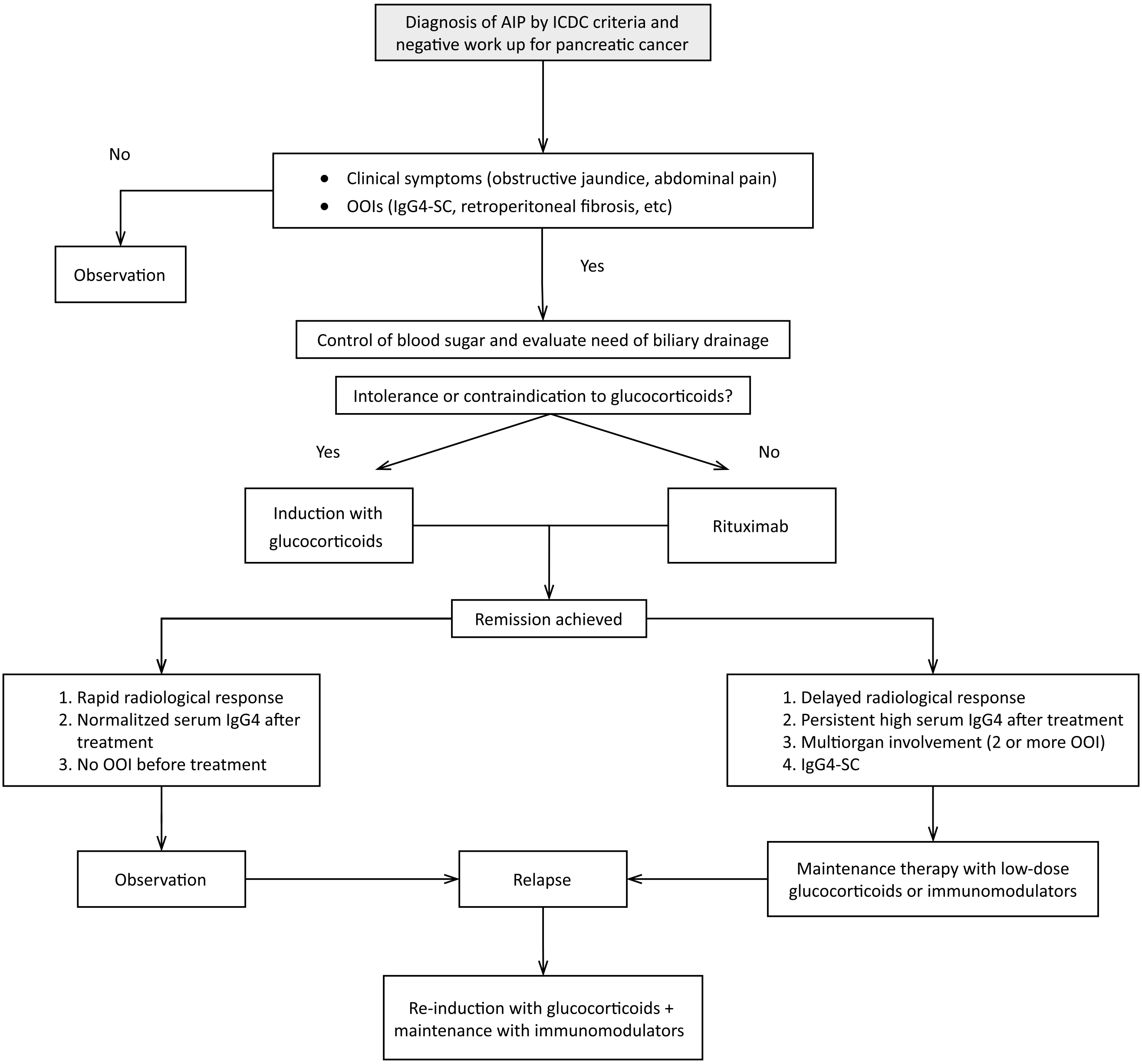
Diagnosis of AIP by ICDC criteria and negative work up for pancreatic cancer
No
Clinical symptoms (obstructive jaundice, abdominal pain)
OOIs (IgG4-SC, retroperitoneal fibrosis, etc)
Observation
Yes
Control of blood sugar and evaluate need of biliary drainage
Intolerance or contraindication to glucocorticoids?
Yes
No
Induction with glucocorticoids
Rituximab
Remission achieved
1. Rapid radiological response
2. Normalitzed serum IgG4 after treatment
3. No OOI before treatment
1. Delayed radiological response
2. Persistent high serum IgG4 after treatment
3. Multiorgan involvement (2 or more OOI)
4. IgG4-SC
Observation
Relapse
Maintenance therapy with low-dose glucocorticoids or immunomodulators
Re-induction with glucocorticoids + maintenance with immunomodulators

Fig. 62.1 Treatment algorithm of AIP based on IAP consensus [18]. *AIP* autoimmune pancreatitis, *ICDC* International Consensus Diagnostiic Criteria, *IgG4-SC* IgG4-related sclerosing cholangitis, *OOI* other organ involvement

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Part VII

Gastrointestinal Autoimmune Diseases

Autoimmune Gastritis

63

Leticia Moreira

Abstract

Autoimmune gastritis is a chronic gastritis that may remain asymptomatic for many years before progressing to gastric atrophy causing depletion of stocks of vitamin B12 and clinical manifestations of pernicious anemia. Autoantibodies to gastric parietal cells, the molecular target of which is the gastric H/K ATPase, are the simplest screening test for autoimmune gastritis. Intrinsic factor autoantibodies, the second autoantibody test, typically segregate with the development of pernicious anemia; these antibodies have two actions—inhibition of vitamin B12 binding with intrinsic factor in the stomach and prevention of its transport into the body via the terminal ileum. As the gastritis evolves, the histology of the stomach shows increasing infiltration by lymphocytes accompanied by increasing destruction of parietal cells and zymogenic cells until the loss of mature cells is complete, the mucosa is atrophic, and there is intestinal metaplasia. This histologic evolution is accompanied by biochemical changes: loss of acid, depletion of pepsinogen I, and increased secretion of gastrin by the gastric antrum. Finally, when the stocks of vitamin B12 are exhausted, clinical and hematologic signs of megaloblastic anemia and its complications become evident. Although immunosuppressive drugs will modulate the autoimmune reaction allowing the maturation of gastric parietal cells, the preferred treatment is vitamin B12 replacement.

Keywords

Gastric atrophy · Vitamin B12 deficiency · Gastric cancer · Endoscopic surveillance · Autoimmune inflammatory condition · Antiparietal cells · Intrinsic factor

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Description of the Disease

Autoimmune gastritis (AIG), also known as autoimmune metaplastic atrophic gastritis (AMAG), manifests as a chronic immune-triggered inflammatory condition. It progressively harms the oxyntic glands and eliminates parietal cells, causing severe gastric mucosal atrophy, intestinal cell transformation (intestinal metaplasia), and elevated levels of gastrin [1]. The absence of parietal cells also hampers the production of intrinsic factors, essential for transporting vitamin B12 for absorption in the terminal ileum. This deficiency leads to a lack of vitamin B12 and the onset of pernicious anemia, the main consequence of AIG.

AIG affects approximately 1–2% of the population, and its frequency appears to have increased in recent decades. It is more prevalent in women, increasing with age, and there might not be any racial predisposition [2].

There is a strong correlation between AIG and other autoimmune conditions like thyroiditis, Sjogren's syndrome, and type 1 diabetes, thus considering AIG as a systemic disease. In this sense, two retrospective cohort studies reported that between 36% and 44% of individuals diagnosed with AIG also exhibited signs of autoimmune thyroiditis. Furthermore, AIG shows a notably higher prevalence among individuals with type 1 diabetes mellitus. Several studies suggest that the likelihood of developing AIG in these individuals is roughly 3–5 times higher compared to the general population [3].

Regarding the physiopathology of this entity, the gastric H/K ATPase ("proton pump") is the molecular target of the humoral and cellular immune response in AIG (Fig. 63.1). Autoantibodies to the gastric parietal cells bind to the 100-kD catalytic (a) subunit and the 60- to 90-kD glycoprotein (b) subunit of the H/K ATPase. Studies of human AIG and of mouse models [4] have led to our current understanding of the destructive role of gastric H/K ATPase-specific Th1 CD4 T cells in the genesis of gastritis and of the protective role of Foxp3-expressing CD4 CD25 regulatory T cells. Moreover, there is a debate surrounding whether infection by *Helicobacter pylori* could act as a catalyst for AIG; also,

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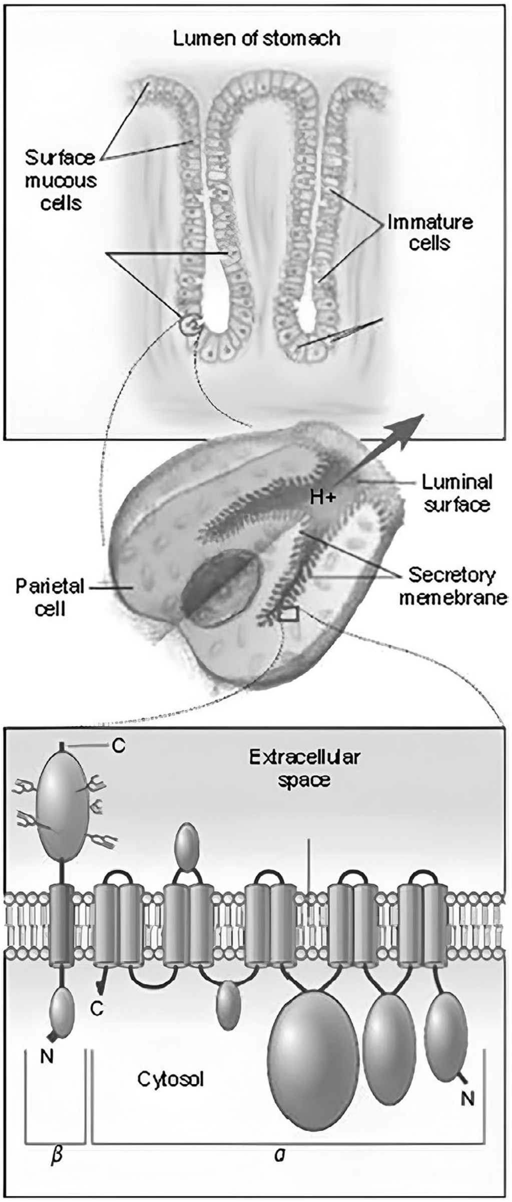

Fig. 63.1 Gastric parietal cell H/K ATPase as the molecular target in autoimmune gastritis associated with pernicious anemia. The top panel represents a gastric gland, showing the location of parietal cells in relation to zymogenic cells, immature cells, and surface mucous cells. The middle panel represents a stimulated gastric parietal cell, showing the lining membrane of the secretory canaliculus on which gastric Hþ/Kþ ATPase is located. The bottom panel represents the catalytic a and glycoprotein b subunits of gastric Hþ/Kþ ATPase, showing their orientation in the lining membrane of the secretory canaliculus of the parietal cell. "N" denotes the N-terminal of protein and "C" the C-terminal of protein. (Reprinted with permission from Toh et al. [1])

some authors suggest there might be a genetic inclination contributing to this association [5].

Clinical Manifestations

AIG is often asymptomatic or associated with mild nonspecific symptoms, leading to a delay in the diagnosis. The median age at diagnosis is 60 years with slightly more women affected than men [6]. The main clinical features of the presentation are listed in Table 63.1.

The usual presentation is with symptoms of anemia due to vitamin B12 deficiency. This vitaminic deficiency leads to atrophic glossitis and megaloblastosis of small intestinal epithelial cells that result in malabsorption and frequent diarrhea. Neurologic complications include peripheral neuropathy and lesions in the postero-lateral columns of the spinal cord (subacute combined degeneration) and in the cerebrum (megaloblastic madness) that progress from demyelination to axonal degeneration and neuronal death. These neurologic complications arise because of the fundamental role of vitamin B12 in central nervous system (CNS) function at all ages, especially the methionine synthase–mediated conversion of homocysteine to methionine essential for nucleotide synthesis and for genomic and non-genomic

Table 63.1 Clinical manifestations of AIG

1. Digestive symptoms:
• Abdominal pain/discomfort: around 50–70%
• Bloating: approximately 30–50%
• Nausea and vomiting: about 20–40%
• Indigestion/dyspepsia: approximately 30–50%
2. Anemia and associated symptoms:
• Fatigue and weakness: approximately 40–60%
• Pallor: around 20–40%
3. Neurological symptoms due to vitamin B12 deficiency:
• Numbness/tingling in hands and feet (peripheral neuropathy): peripheral numbness, muscle wasting, diminished tendon reflexes, loss of perception to light touch and vibration, and spastic ataxia due to peripheral neuropathy and subacute combined degeneration of the spinal cord. Approximately 20–40%
• Cognitive changes: approximately 10–30%
4. Other symptoms:
• Weight loss: around 20–30%
• Diarrhea or constipation: approximately 10–30%
• Loss of appetite and a sore, smooth, and red tongue due to atrophic glossitis

methylation. Complications affecting the CNS are now seldom seen because they occur at the end stage of vitamin B12 deficiency [7].

Risk of Gastric Cancer

Among individuals diagnosed with AIG, two primary categories of gastric neoplasms can potentially arise, namely, gastric adenocarcinoma and neuroendocrine tumors [8]. There is a three-fold excess risk of gastric carcinoma and a 13-fold excess risk for gastric carcinoid tumors associated with hypergastrinemia consequent to achlorhydria. Kamada et al. reported that the development rate of neuroendocrine tumors was 2.4–15.4% and for gastric adenocarcinoma was 0.7–12.2% [9].

Individuals diagnosed with AIG face an elevated risk of type I neuroendocrine tumors, primarily associated with corpus-focused atrophy. The emergence of these tumors stems from the loss of parietal cells, resulting in diminished gastric acid production. This reduction triggers persistent hypergastrinemia, leading to hyperplasia of enterochromaffin-like cells (ECL cells). In a small fraction of cases, this progression can escalate to ECL cell dysplasia and the development of gastric neuroendocrine tumors [10].

Regarding the risk of gastric adenocarcinoma, a meta-analysis indicated a considerable relative risk of 11.05 (with a 95% confidence interval of 6.39–19.11) for the development of gastric cancer in individuals with AIG [11]. Another meta-analysis including 27 studies showed an increased risk of GC of seven-fold in patients with pernicious anemia in comparison with patients without pernicious anemia [11]. The development of gastric adenocarcinoma in this entity is associated with the progression of preneoplastic lesions (gastric atrophy, intestinal metaplasia, and dysplasia) through the known Correa cascade [12] (Fig. 63.2).

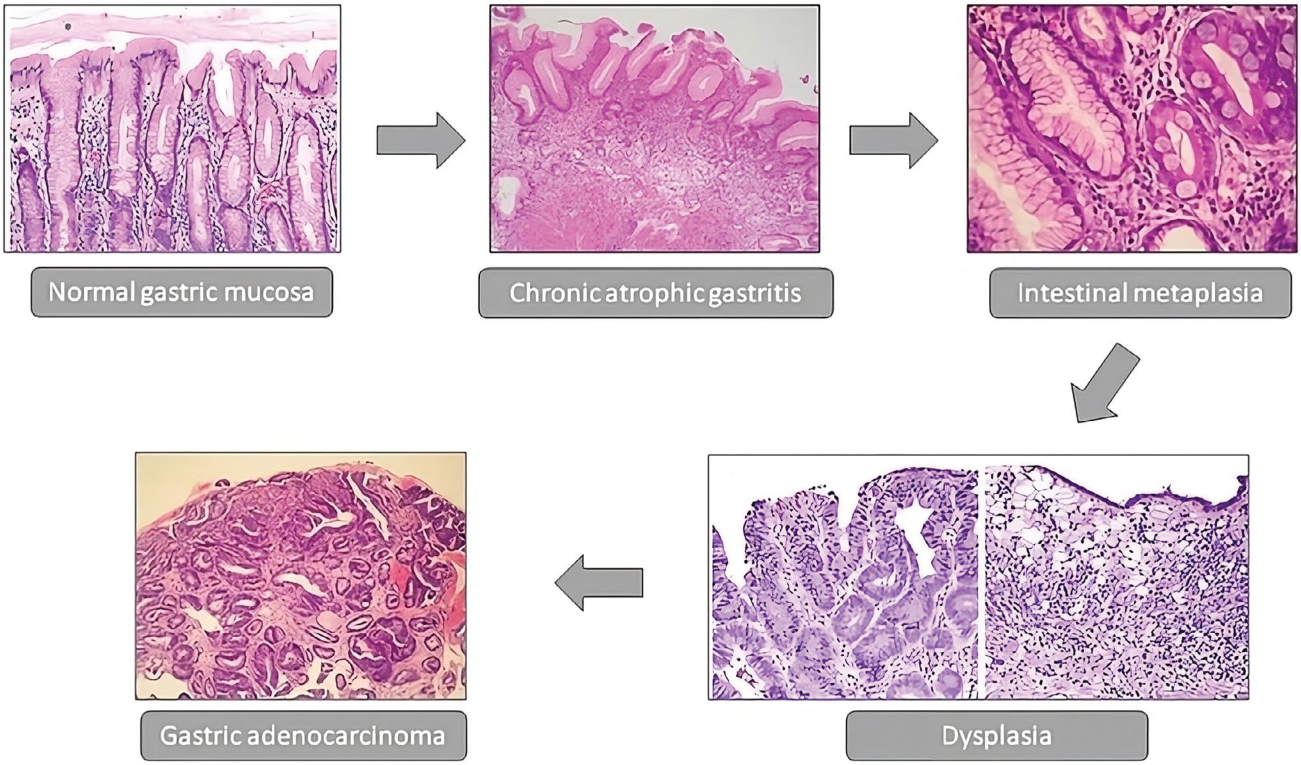

Fig. 63.2 Correa cascade of gastric carcinogenesis

Laboratory Findings

Hematologic Features

The hematologic features are those of low serum vitamin B12 levels and of megaloblastic anemia characterized by peripheral blood features of macrocytosis, hypersegmented polymorphonuclear leukocytes, anemia, leukopenia, thrombocytopenia, or pancytopenia. Bone marrow typically reveals megaloblasts and large myeloid precursors.

A Schilling test, now outmoded but an excellent diagnostic test, will confirm that the vitamin B12 deficiency is the result of intestinal malabsorption due to intrinsic factor deficiency. The low urinary excretion of orally administered vitamin B12 is increased when vitamin B12 is administered with intrinsic factor.

Although anemia usually is macrocytic due to vitamin B12 deficiency, in some cases, there is normocytic or microcytic anemia associated with iron deficiency; this reduced iron absorption due to decreased acid secretion may precede the development of pernicious anemia. This has been attributed to the requirement of gastric acid to reduce iron from its ferric to ferrous form for its absorption [13].

Biochemical Features

Achlorhydria, low levels of serum pepsinogen I, and high levels of serum gastrin are the main biochemical findings in AIG. Hypo- or achlorhydria is indicative of the destruction of the acid-producing gastric parietal cells.

Two types of serum pepsinogen, PG I and PG II, originate from different parts of the stomach. PG I primarily comes from the corpus, while PG II can also be produced in the antrum. Severe atrophy of the gastric body typically leads to reduced levels of PG I (reflecting the destruction of zymogenic cells), while PG II tends to remain relatively higher. Consequently, the PG I/II ratio is generally lower in these circumstances. Establishing a precise cutoff for diagnosis proves challenging since these parameters can also be affected by conditions unrelated to AIG. Nonetheless, cutoff values for PG I less than 70 and a PG I:II ratio less than or equal to 3 are commonly employed. These cutoffs demonstrate good discriminative ability, particularly in identifying moderate to severe corpus atrophy [14].

Finally, hypergastrinemia is the result of sparing of the antrum from the autoimmune reaction and stimulation of the gastrin-producing G cells by the loss of acid-producing gastric parietal cells.

Table 63.2 Main laboratory findings in AIG

Vitamin B12 deficiency	Around 70–90% of patients may have reduced serum B12 levels
Parietal cell antibodies	Approximately 70–90% of cases may test positive for parietal cell antibodies
Intrinsic factor antibodies	Presence in roughly 50–70% of patients
Gastrin levels	Elevated in about 60–80% of cases due to decreased acid production
Iron deficiency anemia	Seen in around 20–40% of cases due to impaired iron absorption
Red blood cell morphology	Presence of megaloblastic or macrocytic cells in about 30–50% of affected patients
Serum pepsinogen 1 levels	Decreased levels in some cases, but percentages may vary widely

Serum Antibodies

Serum antibodies to gastric parietal cells and to intrinsic factor remain the mainstay for the serologic diagnosis of AIG and pernicious anemia.

PCAs (parietal cell antibodies) direct against the gastric H/K ATPase and demonstrate higher sensitivity, making them more adept at detecting the presence of the condition. Regarding IFAs (intrinsic factor antibodies), two specificities have been identified: one reacts with the vitamin B12 binding site and the other impedes the transport of vitamin B12 through the mucosa of the terminal ileum. Thus, these two specificities play a major role in the malabsorption of vitamin B12 and the development of pernicious anemia. IFAs are more specific than PCAs but exhibit lower sensitivity (with a wide variation range). Specifically, PCA boasts a sensitivity of 81% and a specificity of 90%, whereas IFA displays a sensitivity of 27% and a specificity of 100% (Table 63.2).

Endoscopic Findings

Upper gastrointestinal endoscopy can reveal distinctive observations in patients with AIG. The examination highlights the loss of gastric folds, a pale appearance of the mucosa, and the prominence of blood vessels visible through the thinned mucosa. Severe atrophy, particularly in the corpus, becomes evident with the visibility of mucosal blood vessels. Additionally, there is the presence of adherent dense mucus, which appears pale yellow to white in the upper gastric body and fundus. This mucus tends to cling persistently, making it challenging to remove even with

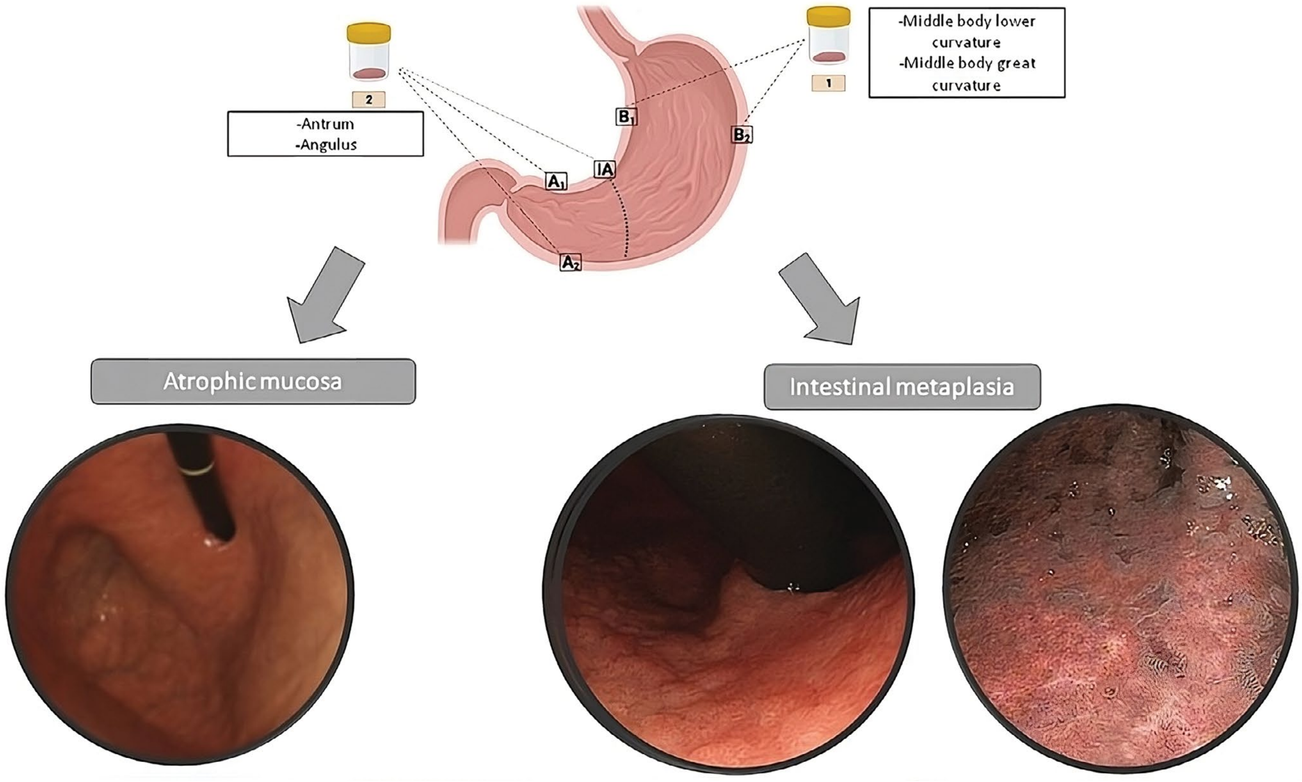

Fig. 63.3 Sydney biopsy protocol for gastric preneoplastic identification and surveillance by upper gastrointestinal endoscopy

water washing due to reduced gastric juice secretion and mucosal atrophy.

Additional frequent observations include hyperplastic polyps and oxyntic mucosa pseudopolyps often multiple and mainly found in the corpus, occurring more frequently in advanced stages of AIG, due to severe atrophic mucosa. Magnifying endoscopy reveals characteristic features like the “White Globe Appearance” (WGA) and “Cast-Off Skin Appearance” (CSA) [15].

To maximize diagnostic accuracy and assess the severity and extent of the disease and detection of preneoplastic lesions (atrophy, intestinal metaplasia, and dysplasia), the Sydney protocol is recommended to take systematic gastric biopsies (Fig. 63.3). This approach allows for comprehensive histological evaluation and utilizes the operative link for gastritis assessment (OLGA) and operative link for gastric intestinal metaplasia (OLGIM) staging systems for atrophy and intestinal metaplasia, respectively [16, 17].

Histological Findings

AIG presents distinct histological features. It primarily showcases atrophy in the oxyntic mucosa, known as corpus-predominant atrophic gastritis. This atrophy may or may not be accompanied by the replacement of tissue by metaplastic mucosa. Traditionally, the architecture of the antral mucosa remains intact, although in advanced stages or in cases where there is concurrent *Helicobacter pylori* infection, this preservation might not be evident.

AIG is characterized histologically by a mononuclear cellular infiltrate in the submucosa that extends into the lamina propria between the gastric glands accompanied by degeneration of mature parietal cells and zymogenic cells. In the established lesion, there is a marked reduction in the number of gastric glands, and the parietal cells and zymogenic cells are lost from the gastric mucosa and replaced by mucus-containing cells (intestinal metaplasia).

Diagnostic Criteria

Detecting AIG presents various challenges. The absence of specific symptoms and the similarity of its symptoms to other gastrointestinal conditions like peptic ulcer disease, functional dyspepsia, and acid reflux make it difficult to diagnose based solely on clinical presentation. Biopsy of the gastric mucosa is essential for confirmation, but acquiring adequate samples can be tricky, especially in cases of mild or early-stage inflammation, and also, the finding is not specific to AIG. As mentioned in the previous section, there is not a unique and specific finding pathognomic of AIG, and the sensitivities and specificities of the different markers, such as clinical manifestations, laboratory, endoscopic, and histopathological findings, vary markedly, so these values should be interpreted cautiously.

Traditionally, diagnosing this condition involves a combination of clinical and laboratory findings, eventually confirmed by identifying characteristic histopathological changes. Laboratory data utilized for screening or diagnosis includes assessing autoantibodies, serum pepsinogen levels, and gastrin levels [14]. Establishing internationally recognized diagnostic criteria remains an ongoing challenge in the field, and a universally accepted set of diagnostic criteria can be challenging due to several reasons:

1. Variability in presentation: Autoimmune gastritis can manifest with a wide spectrum of symptoms and severity, ranging from asymptomatic to severe complications. This variability in presentation makes it difficult to establish a rigid set of criteria applicable to all cases.
2. Complexity of diagnostic tests: Diagnosis often involves a combination of serological markers (such as parietal cell antibodies and intrinsic factor antibodies), endoscopic evaluation, histopathological examination, and clinical correlation. Differentiating autoimmune gastritis from other gastric conditions requires integrating various test results and clinical information.
3. Overlap with other conditions: Some features of autoimmune gastritis may overlap with other gastrointestinal disorders, making it challenging to define specific criteria that solely apply to autoimmune gastritis without potentially misdiagnosing or overlooking other conditions.

Although there are recognized diagnostic markers, as previously discussed, there are no internationally accepted criteria for the diagnosis of either autoimmune gastritis or pernicious anemia. Thus, for autoimmune gastritis in asymptomatic subjects, we suggest that the presence of parietal autoantibody could be diagnostic of the underlying gastric pathology. For pernicious anemia, we suggest fulfillment of a minimum of all these criteria: (a) parietal cell and/or intrinsic factor antibodies; (b) anemia and macrocytosis; and (c) low serum levels of vitamin $B_{12.}$

Treatment and Surveillance

Although immunosuppressive drugs will modulate the autoimmune reaction allowing maturation of gastric parietal cells, the preferred treatment is vitamin B12 replacement. The standard treatment is monthly intramuscular injections of at least 100 mg of vitamin B12 to correct the vitamin deficiency and the complications, particularly neurologic complications. There is recent interest in oral treatment with vitamin B12 on the grounds that about 1% of the vitamin is absorbed by mass action in the absence of intrinsic factor. The evidence derived from limited studies of randomized controlled trials comparing the effectiveness of oral versus intramuscular vitamin B12 to treat vitamin B12 deficiency suggests that 2000 mg doses of oral vitamin B12 daily and 1000 mg doses initially daily and thereafter weekly and then monthly may be as effective as intramuscular administration in obtaining short-term hematologic and neurologic responses in vitamin B12–deficient patients [18].

Surveillance for AIG, typically involves MAPS II upper gastrointestinal endoscopic follow-ups every 3–5 years, with gastric biopsies to rule out preneoplastic lesions, gastric polyps, neuroendocrine tumors, and gastric adenocarcinoma. These check-ups encompass assessing the frequency of interval surveillance and keeping a watch on deficiencies in vitamin B12, folic acid, and iron [19].

However, it is essential to note that there is a lack of randomized controlled studies assessing the advantages of endoscopic surveillance. Moreover, there is no established consensus on the ideal intervals or methods for surveillance in AIG specifically aimed at early detection of neoplasia, such as dysplasia or cancer.

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Ulcerative Colitis

64

Elena Ricart

Abstract

Ulcerative colitis is a lifelong inflammatory disease affecting the rectum and colon to a variable extent that occurs in people with a genetic predisposition following environmental exposures that lead to gut epithelial barrier defects and a dysregulated immune response. Patients usually present with bloody diarrhea, and the diagnosis is based on a combination of clinical, biological, endoscopic, and histological findings. The aim of medical treatment is to induce a rapid clinical response and to maintain clinical and endoscopic remission to prevent long-term disability. Treatments include 5-aminosalicylic acid drugs, thiopurines, biologics (e.g., anti-cytokines and anti-integrins), and small molecules (Janus kinase inhibitors and sphingosine-1-phosphate receptor modulators). Although the therapeutic options are expanding, 10–20% of patients still require proctocolectomy for medically refractory disease.

Keywords

Inflammatory bowel disease · Ulcerative colitis · Crohn's disease · Diagnosis · Treatment

Description of the Disease

Inflammatory bowel disease (IBD) encompasses a group of digestive tract disorders, with a chronic course and incompletely understood pathogenesis that mainly includes ulcerative colitis (UC) and Crohn's disease (CD). UC is a lifelong inflammatory process limited to the colon characterized by continuous involvement of the colonic mucosa from the rectum to a variable proximal extension thereof. Typically marked by periods of activity and remission, it tends to manifest with flares of variable severity. In recent years, a significant increase in its incidence has been observed in both developed and developing countries. Although it can appear at any age, it is more frequent in young adults, conferring important socio-economic-health consequences. UC has a multifactorial etiology, with a genetic predisposition associated with environmental factors such as diet, smoking, exposure to microbes, and other not well-defined factors that act as triggers for the disease causing a loss of homeostasis between host bacterial antigens of the intestinal microbiota and the patient's immune system that cause the disruption of the mucosal barrier, translocation of antigens to the lamina propria, and the induction of an aberrant acute and chronic inflammatory response that is perpetuated over time [1]. The diagnosis is based on a set of clinical, laboratory, endoscopic, and histological data. Early diagnosis of UC and the initiation of adequate treatment are crucial to improve the prognosis and well-being of affected individuals.

Clinical Manifestations

The main clinical symptoms of UC include diarrhea with blood and mucus, urgency, and abdominal pain with negative stool cultures [2]. The intensity of these symptoms and signs typically corresponds to the severity and extent of the disease. Almost invariably, the rectum is affected, leading to urgency and tenesmus. In cases limited to the rectum, stools might appear normal, occasionally even leading to paradoxical constipation. When the involvement is extensive and severe, stools are liquid and frequent, with blood and mucus, and abdominal pain may appear. In moderate-severe cases, there may be fever and a decline in overall general condition. Symptoms are often present for weeks before medical advice is sought, and digestive symptoms for more than 4–6 weeks allow differentiation of UC from most cases of infectious diarrhea. Mild cases may present as unremarkable upon

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examination, whereas, in severe cases, abdominal distension and diffuse pain can be present. In the most severe cases, there may be fever, tachycardia, and hypotension. The set of symptoms and signs of the disease, together with basic complementary examinations [hemoglobin, serum albumin, C-reactive protein (CRP)] and radiological tests (simple abdominal X-ray, CT scan), make it possible to reliably establish the diagnosis and the severity of the flare, which has crucial therapeutic and prognostic implications. Diverse indices exist for quantifying disease activity, incorporating both clinical and analytical parameters, albeit without full validation. The original Truelove–Witts Index and, more recently, the modified one are usually the most used in clinical practice and have also been adapted to the Montreal classification [3].

Extraintestinal manifestations can be observed in up to 50% of UC patients over the disease course. These extraintestinal manifestations include inflammatory conditions located outside the gastrointestinal tract. They are either mediated by the same immunological mechanisms as UC or distinct independent mechanisms. Extraintestinal manifestations associated with UC include peripheral spondyloarthropathy; ocular manifestations such as uveitis and episcleritis; mucocutaneous manifestations such as erythema nodosum, pyoderma gangrenosum, pyostomatitis vegetans, or Sweet's syndrome; and hepatic diseases such as primary sclerosing cholangitis (PSC).

Furthermore, various immune-mediated disorders linked to IBD include axial spondyloarthropathy (ankylosing spondylitis and sacroileitis), psoriasis, hidradenitis suppurativa, vitiligo, and vasculitis. Finally, a range of extraintestinal complications related to IBD or arising from UC therapies include thromboembolic events, osteoporosis, angular cheilitis, nephrolithiasis, amyloidosis, and biologic drug-induced paradoxical psoriasis.

Biochemical and Serological Features

Distinctive biochemical markers for IBD are lacking, and blood tests are often normal in inactive UC patients. However, these tests play a pivotal role in uncovering potential hematological or biochemical abnormalities and assessing and monitoring disease activity. Elevated erythrocyte sedimentation rate (ESR), CRP, anemia, leukocytosis, and thrombocytosis commonly are present during flares. Of these, the most frequently used marker for monitoring inflammatory activity is CRP, which has a sensitivity of 50% for active UC. Blood loss in feces or medullary iron blockage due to prolonged inflammation can lead to hypochromic microcytic anemia. During severe activity, serum albumin levels typically decline, attributed to malnutrition, heightened catabolism, and protein losses via the digestive tract. Liver function assessments may exhibit cholestasis in instances of pronounced malnutrition or concurrent PSC. The measurement of fecal calprotectin (FC), a protein abundant in neutrophil cytoplasm, shows high sensitivity and specificity for distinguishing between UC and functional conditions (positive predictive value of 90%). It is also a good marker for uncovering subclinical activity during follow-up. Notably, the diagnostic precision of FC surpasses that of CRP. FC values under 150 mg/kg are highly sensitive (79%) and specific (75%) for endoscopic remission. However, FC values exhibit considerable variability in moderate-to-severe activity cases, even across different stools from the same patient. Consequently, fecal calprotectin is a reliable indicator of activity but not severity.

Over time, various serological tests such as a perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA), anti-*Saccharomyces cerevisiae* antibody (ASCA), Omp-c, and c-byr, among others, have been used to try to help physicians in either the initial diagnosis of IBD or to identify subgroups of CD or UC patients with a specific clinical course. Despite their potential utility, especially in cases of indeterminate colitis, their broad acceptance and integration into clinical practice remain limited. Notably, p-ANCA and ASCA assessments could assist in distinguishing between CD (ASCA positive) and UC (p-ANCA positive).

Diagnostic Criteria

The diagnosis of UC relies on a comprehensive assessment encompassing clinical data, laboratory findings, endoscopic evaluation, and histological parameters, as outlined in the Lennard-Jones criteria [4], but there is no gold standard. The main diagnostic features of UC are summarized in Table 64.1.

Bacterial colitis needs to be investigated and includes infection from *Campylobacter* spp., *Salmonella* spp., *Shigella* spp., *Yersinia* spp., and, more rarely, enterotoxigenic Escherichia coli. Stool cultures and *Clostridioides difficile* toxin testing should be used to systematically rule out infection at diagnosis and also at every disease flare-up to rule out concomitant infectious exacerbation.

Besides clinical, biochemical, and serologic features already discussed, the endoscopy is the most accurate diagnostic tool to evaluate mucosal lesions and also allows biopsies to be taken. Colonoscopy plays a crucial role in distinguishing between CD and UC, as well as aiding in differential diagnoses with other conditions. For diagnostic purposes, a complete colonoscopy is necessary, encompassing ileoscopy with at least two biopsies from each segment (ileum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum). This comprehensive approach aids in determining the location and extent of lesions which is essential for guiding therapeutic decisions and prognostic

Table 64.1 Diagnostic criteria of ulcerative colitis

Clinical features	Haematochezia (>90%) Bloody diarrhea (>80%) Rectal tenesmus Fecal urgency/incontinence Abdominal pain Fever Extraintestinal manifestations
Laboratory features	Elevated CRP and ESR Anemia Elevated FC Thrombocytosis Hypoalbuminemia
Endoscopic features	Diffuse and continuous mucosal involvement from the rectum to a proximal variable extent Erythema, edema, and loss of vascular pattern Erosions, ulcers, and friability Pseudopolyps Loss of haustration
Histological features	Crypt distortion, branching, and atrophy Crypt abscesses Increased mononuclear inflammation in lamina propria Mucin depletion

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *FC* fecal calprotectin

assessments. At endoscopy, active UC typically exhibits characteristic features, including an erythematous, friable mucosa with a granular surface, and loss of the normal vascular pattern. In severe flares, erosions (≤5 mm in diameter) and ulcerations (>5 mm in diameter) arise, primarily on inflamed mucosal areas (Fig. 64.1). Lesions generally initiate in the rectum and extend continuously upwards, potentially reaching the cecum. The long-lasting disease often leads to luminal narrowing and loss of haustration, resulting in a tubulized, shortened colon appearance.

The most widely used endoscopic index to quantify the severity of UC is the Mayo Index, with a score range from 0 (remission) to 3 (severe disease). Another relevant index, the Ulcerative Colitis Endoscopic Index of Severity (UCEIS), has been developed and validated more recently. UCEIS integrates parameters like vascular pattern, mucosal bleeding, and ulcerations into its scoring system [5, 6]. Both indices assess the segment with the most severe lesions.

At histology, UC presents with a chronic inflammatory infiltrate involving lymphocytes and plasma cells, along with an acute infiltrate containing neutrophils, commonly observed within crypt lumens, contributing to crypt abscesses. Characteristically, the crypts have a reduced number of mucoid cells, with distortion and branching at the base. When disease activity decreases, spontaneously or upon treatment, the inflammatory infiltrate is reduced, crypt abscesses disappear, and the mucoid cell population recovers. However, crypt architecture remains altered, with shortened, branched, or even absent crypts [7]. In a minority of cases (<10%), a severe manifestation might emerge with colonic dilation (toxic megacolon) or perforation. In this scenario, the colonic wall thins, and large denuded areas of mucosa appear. The exposed muscle layer could exhibit fissures extending to the serosa. In such instances, inflammation might encompass all layers of the colon [8].

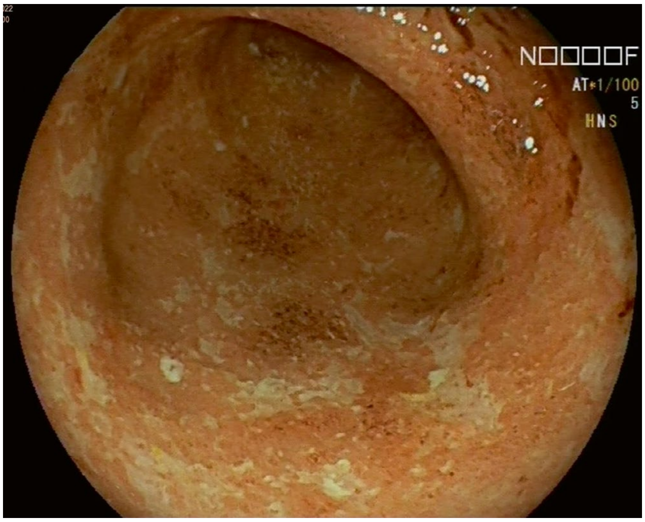

Fig. 64.1 Endoscopic image of a patient with ulcerative colitis showing an erythematous mucosa, with complete disappearance of the vascular pattern. Superficial ulcers coated with fibrin are evident, along with mucosal friability

Prognosis

In general, the life expectancy of individuals with UC is comparable to that of the general population. Following diagnosis, around 30% of patients with distal UC may experience extension flares, occasionally severe and unresponsive to treatment. Roughly 50% of patients present a progressive decrease in disease activity, while 30–40% encounter episodic flares. It is estimated that between 20% and 30% of patients require a surgical approach over time, with persistent activity refractory to medical treatment being the most frequent indication [9]. Patients with colonic IBD have a higher risk of developing colorectal cancer (CRC) compared to the general population. Risk factors for CRC in both UC and CD include a disease duration surpassing 8–10 years, extensive disease involvement (beyond the rectum in UC or more than 30% of the colon in CD), co-occurrence of PSC, a family history of CRC, and sustained uncontrolled chronic colonic inflammation. Notably, individuals with PSC have an increased risk for CRC from the time of UC diagnosis [10]. Surveillance colonoscopy should be performed periodically in UC patients starting 8–10 years after diagnosis and yearly since diagnosis if PSC is present [11].

Prediction

The strongest risk factor for UC development is having a first-degree relative affected by the condition. Among the most extensive studies, the risk is estimated at 15–20% in monozygotic twins [12]. Notably, breastfeeding and tobacco use emerge as protective elements against disease onset, substantiated by robust evidence [13, 14]. Several other risk factors have been examined, although with less substantial evidence. These include dietary factors, hormonal therapies involving estrogens, personal hygiene practices, antibiotic usage, and the use of anti-inflammatory medications, among others [15]. The inability to predict disease onset or clinical phenotype hinders routine clinical applicability.

Therapy and Prevention

The main objective of medical treatment is to induce and maintain clinical remission and mucosal healing without corticosteroids in order to prevent disease progression and disability associated with relapsing chronic disease, avoid surgery and cancer, and maintain a good quality of life. The extent of the disease should be taken into account when designing treatment strategies for UC, as this can influence the most suitable approach for drug administration. Typically, disease extent is categorized based on involvement limited to the rectum (proctitis), disease extending distal to the splenic flexure (left-sided UC), or disease encompassing areas proximal to the splenic flexure (extensive UC). Thus, treatment strategy must be tailored according to the location of lesions, flare severity, and response to prior or concurrent treatments or concurrent medical conditions [16]. A comprehensive overview of available drugs for UC treatment is presented in Table 64.2.

In specific scenarios such as toxic megacolon, cases of fulminant colitis, or for treating or preventing colon cancer, total proctocolectomy with ileal pouch-anal anastomosis might be necessary [17].

Multiple environmental and dietary factors might affect the risk of developing UC, and although the precise mechanisms are unclear, many are implicated in the rising global incidence. The strength of these epidemiological associations is variable, and the mechanistic reasons are poorly understood. If causal relationships do exist, then lifestyle and dietary modifications could be featured in future disease prevention strategies [18].

Table 64.2 Available therapies for UC

	Drugs	Indication
Aminosalicylates	Sulfasalazine Mesalazine	Induction and maintenance of remission
Steroids	Systemic (prednisone, prednisolone, hydrocortisone)	Induction of remission
	Topical (beclometasone dipropionate)	Induction of remission
Immunomodulators	Thiopurines	Maintenance of remission
	Cyclosporine	Induction of remission
Anti-TNF	Infliximab Adalimumab Golimumab	Induction and maintenance of remission
Anti-integrins	Vedolizumab	Induction and maintenance of remission
Anti-IL12/IL23	Ustekinumab	Induction and maintenance of remission
JAK inhibitors	Tofacitinib	Induction and maintenance of remission
S1P receptor modulator	Ozanimod	Induction and maintenance of remission

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Crohn's Disease

65

Agnès Fernández-Clotet

Abstract

Crohn's disease (CD) is a chronic inflammatory bowel disorder, characterized by a wide spectrum of disease phenotypes that typically alternates periods of active inflammation and remission. Its etiology is unknown and characterized by leukocyte infiltration of the bowel wall which results in intestinal ulceration, causing diarrhea, abdominal pain, rectal bleeding, and weight loss, among many other symptoms. CD pathophysiology is very complex, requiring a genetic predisposition, the influence of certain environmental factors, and a dysregulated immune system, as effector elements. There are no pathognomonic signs or symptoms of CD; therefore, its diagnosis has to be based on a convincing combination of symptoms, biochemical abnormalities, mucosal endoscopic findings, histological examination of mucosal biopsies, and imaging findings. It also requires ruling out other entities, such as infectious colitis, celiac disease, or drug-induced enterocolitis. Treatment of CD included the use of steroids, immunosuppressants, and biological drugs (with different mechanisms of action). However, medical therapy is far from satisfactory, and a significant proportion of patients still require surgical treatment especially when there are complications like abdominal stenosis or fistula.

Keywords

Bowel · Crohn's disease · Diagnosis · Inflammation · Inflammatory bowel disease

Description of the Disease

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract that is characterized by periods of clinical activity and remission and, consecutively, can result in progressive bowel damage and disability. CD can affect individuals of any age, from children to the elderly (with a high incidence between 20 and 40 years), with a high impact on health-related quality of life [1].

CD pathophysiology is very complex, requiring a genetic predisposition, the influence of certain environmental factors, and gut microbiota disbalance that in combination lead to a dysregulation of innate and adaptive immune response that compromised epithelial intestinal barrier function [2]. Smoking, a family history of inflammatory bowel disease, and recent infectious gastroenteritis are well-known risk factors for developing the disease. As the precise etiology of CD remains unknown, curative therapy is not yet available [2].

The prevalence and incidence of CD are increasing in adults and children, and they are greater in the Western world, developing countries, and urban areas (compared to rural areas). Prevalence in Europe is 322 per 100,000 inhabitants, and incidence in northern Europe is 10.6 per 100,000 inhabitants [3].

Assessment of disease extent and ruling out the presence of complications is paramount to guiding therapeutic decisions. CD is characterized by transmural wall inflammation, typically segmental and asymmetrical, and can affect from the mouth to the anus. It is typically located in the small bowel, in the colon, or a combination of both. However, the most commonly affected segment is the terminal ileum, alone or in combination with the colon [4]. It can also affect the anus and perianal tract, leading to fistulas, abscesses, or ulcers. Disease phenotype is not a stable characteristic in CD patients: it usually starts with inflammatory lesions (in 75% of cases), but up to one-third of patients present with complicated behavior (strictures, fistula, or abscesses) at diagnosis. Most patients over time will develop complications: after 10 years, 30% persist with inflammatory behavior compared

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Table 65.1 Montreal classification of Crohn's disease

Age at onset	A1: diagnosed at the age of 16 years or before A2: diagnosed at the age of 17–40 years A3: diagnosed above 40 years
Disease location	L1: ileal L2: colonic L3: ileo-colonic + L4 (if it exists, location proximal to terminal ileum)
Disease behavior	B1: inflammatory B2: stricturing B3: penetrating +p (if it exists, perianal disease)

to stricturing and fistulizing (32% and 37%, respectively), which can lead to progressive damage to the gastrointestinal tract and significant disability, with roughly 50% of patients requiring surgery within 10 years of diagnosis [5]. The combination of variables such as the age at onset, the location, and the behavior course is included in the Montreal classification (Table 65.1) which also has prognostic implications [5].

The inflammatory effect of CD can extend beyond the gastrointestinal tract and can affect organs outside the intestinal lumen and may result in extraintestinal complications. Areas affected included the eyes, hematologic system, joints, and skin. Extraintestinal manifestations can occur in 50% of patients with CD, and they can even precede the digestive symptoms, although it is rare [6].

Clinical Manifestations

Clinical manifestations are very heterogeneous and depend on disease extension, severity, behavior, or presence of extraintestinal manifestations. Some patients may have symptoms for years before the diagnosis of CD. The most frequent symptoms are diarrhea (>6 weeks), abdominal pain, and weight loss. Fatigue and anorexia are common symptoms too [7]. These symptoms should raise the suspicion of CD, especially in young patients with delayed growth. In patients with colonic inflammation, rectal bleeding or bloody diarrhea might be the major symptoms, and in patients with gastroduodenal inflammation, anorexia, nausea, and vomiting might be present. A high fever should always raise the suspicion of a septic complication. CD is most often present insidiously but can also appear as an acute toxic illness with signs of acute peritonitis [8]. Table 65.2 summarizes the main symptoms related to CD.

Complication forms of disease like bowel obstructions are characterized by lack of flatus and bowel movements, hyperactive bowel sounds, nausea, and vomiting. Patients with penetrating CD can develop fistula or abscesses: when an abscess is present, in addition to abdominal pain, patients can have systemic symptoms such as fever and chills.

Table 65.2 Symptoms related to Crohn's disease

Symptom	Frequency (%)
Diarrhea	80
Abdominal pain (>3 month)	70
Delayed growth (in children and adolescents)	65–85
Fatigue	54
Weight loss (5% of usual body weight)	50
Rectal bleeding	40–50
Perianal disease	35
Extraintestinal manifestations	17

The medical history should identify specific findings for CD, identify alternative diagnosis (celiac disease, infections, irritable bowel syndrome, ischemic colitis, chronic pancreatitis, diverticulitis or colorectal cancer), and search for extraintestinal manifestations [9].

Physical examination findings include abdominal tenderness, distension, and/or masses and also signs of malnutrition, anemia, or malabsorption. An anorectal exploration and pelvic examination are required to rule out abscesses, fissures, or fistulas [2].

Laboratory Findings

There are no specific biochemical markers, and the blood test is often normal in inactive CD. On the other hand, when there is a flare, check for signs of acute and/or chronic inflammatory response, anemia, fluid depletion, and signs of malnutrition. Initial laboratory investigations should include C-reactive protein, full blood count, basic metabolic panel, erythrocyte sedimentation rate, liver function tests, iron studies, vitamin B12, and vitamin D levels. Elevated C-reactive protein and erythrocyte sedimentation rate are standard laboratory surrogates of the acute phase response to inflammation. Hypoalbuminemia and vitamin deficiencies (folate, iron, 25-hydroxyvitamin D, and vitamin B12) might be present in extensive small bowel disease. Anemia and thrombocytosis represent the most common changes in the full blood count [10]. The most common etiologies for anemia in CD include iron deficiency, anemia of chronic disease, and vitamin B12 deficiency.

Stool biomarkers, like fecal calprotectin (that correlate with neutrophil infiltrates in the gut and represent a marker or intestinal inflammation), are being used as a screening test and to assess disease activity. The cutoff point for differentiating mucosal inflammation is assay-dependent and might vary between 50 and 250 μg/g [11]. A recent meta-analysis confirmed that low C-reactive protein and/or low calprotectin have a 99% negative predictive value for irritable bowel syndrome when considering the diagnosis of inflammatory bowel disease [12]. Table 65.3 summarizes the main laboratory findings related to CD.

Table 65.3 Laboratory findings related to Crohn's disease

C-reactive protein ≥5 mg/L	Sensitivity 49%, specificity 92%
Anemia (hemoglobin <13 g/dL in men and <12 g/dL in non-pregnant women)	Prevalence 9–74%
Calprotectin ≥50 μg/g	Sensitivity 88%, specificity 72%

If diarrhea is present, stool should be tested for enteric pathogens, parasites, and *Clostridium difficile* toxin [13].

Serological Markers

For many years, a number of serological tests, including antibodies against *Saccharomyces cerevisiae* (ASCAs), anti-neutrophil cytoplasmic antibodies (ANCAs), antibodies directed against Omp-C, anti-flagellin (CByr1), and many others, have been used to try to help physicians in either the initial diagnosis of inflammatory bowel disease or to identify subgroups of CD or ulcerative colitis. Although they might be of some help, especially in cases of indeterminate colitis, they have not reached wide acceptance and use in clinical practice. The serological combination of ASCA-positive/ANCA-negative was found to have a limited value for the diagnosis of CD with a sensitivity of 86.91%, a specificity of 41.07%, and a low positive predictive value of 52.51% [14]. Table 65.4 summarizes the serological markers related to CD.

About 60–70% of patients might have antimicrobial antibodies in their serum, the most prevalent being anti-*Saccharomyces cerevisiae* antibody IgA. The sensitivity and specificity of these antibodies are too low for diagnostic purposes. However, patients who present with high titles and increasing numbers of positive markers have an increased likelihood of developing more aggressive phenotypes [15].

Despite the major advances in the field of CD genetics, there are currently no genetic tests recommended routinely for diagnosis [13].

Diagnostic Criteria

There are no pathological features that can be considered as completely specific to CD. For that reason, diagnosis of CD mainly relies on a combination of clinical suspicion with suggesting symptoms, with typical endoscopic, histological, radiological, and/or biochemical findings, along with the process of ruling out other conditions. History, physical examination, and basic laboratory findings drive the decision to pursue the diagnosis [13].

Endoscopy remains the first-line procedure for the diagnosis of CD and a complete colonoscopy with ileoscopy is recommended. The endoscopic hallmark of CD is the patchy distribution of inflammation with skip lesions. Segmental inflammation, edema, aphthous ulcers, and longitudinal ulceration are typical findings. Criteria of severity are defined as deep ulcerations eroding the muscle layer or mucosal detachments or ulcerations limited to the submucosa but extending more than one-third of a defined colonic segment [13]. Upper endoscopy is not routinely recommended in adults with CD without upper gastrointestinal symptoms. Diagnostic small bowel capsule endoscopy is reserved for cases in which endoscopic studies have been negative despite suggestive symptoms of inflammatory bowel disease [13].

Histological examination of mucosal biopsies is recommended, and biopsies from the terminal ileum as well as each colonic segment are mandatory. Suggestive histological features include chronic focal, discontinuous, patchy, and transmural inflammatory infiltrate and goblet cell preservation. Transmural lymphoid aggregates and pyloric gland metaplasia are common findings. The histological hallmark of CD is the epithelioid granuloma, which is seen in only about 15% of mucosal biopsies but in up to 70% of cases in surgical specimens [16].

Cross-sectional imaging tests such as ultrasonography, CT enterography, or magnetic resonance enterography are complementary to endoscopy and offer the opportunity to assess mural and extramural involvement; that is the reason why they have gained increasing importance in the management of CD. When available, ultrasonography or magnetic resonance enterography should be preferred to reduce the risk of cumulative radiation exposure. A radiological exam should be done at diagnosis to assess the extent of the disease and the presence of complications such as strictures or fistulas, thereby providing information about disease behavior. Patients with perianal CD should be assessed with pelvic magnetic resonance for accurate assessment [17].

The criteria of Lennard-Jones to uniform the diagnosis of CD have been widely accepted and defined macroscopic and microscopic criteria. The macroscopic diagnostic tools include physical examination, endoscopy, radiology, and examination of an operative specimen. Microscopic features can be only partly assessed on mucosal biopsy but more completely assessed on an operative specimen. The diagnosis depends on the findings of discontinuous and often granulomatous intestinal inflammation. The diagnosis is established if granuloma is found at pathological examination +1 other criteria or in the absence of granuloma in the pathological examination the presence of three other criteria (Table 65.5) [18].

Table 65.4 Serological markers related to Crohn's disease

Serological marker	Immunoglobulin class	Prevalence (%)	Sensitivity (%)	Especificity (%)
ASCA	IgA and/or IgG	60–70	37–72	82–100
pANCA	IgG	10	52	91
Anti-OmpC	IgA	24–55	20–55	81–88
Anti-Cbir 1	IgG	50–56		

Table 65.5 Lennard-Jones criteria to diagnose Crohn's disease

Physical examination	Abdominal pain Diarrhea Weight loss Abdominal mass Fever Perianal disease Extraintestinal manifestations
Endoscopy findings	Inflammatory lesions: aphthous ulcers, large ulcers, inflammatory polyps, and edema Stenosis and fistula
Radiology findings	Colon involvement: with inflammatory lesions (ulcers, stenosis, fistula) typically with segmentary distribution Ileon involvement: ulcers and stenosis
Examination of an operative specimen	Major criteria: transmural inflammation and granuloma Minor criteria: mucin retention and lymphoid aggregates

Criticism on the Diagnostics Criteria

CD's diagnosis can sometimes be challenging because it is a heterogeneous entity comprising a variety of complex phenotypes in terms of disease location, severity of inflammation, and disease behavior. A single gold standard test is not available. The current view is that the diagnosis is established by a non-strictly defined combination of clinical presentation, typically endoscopic, histological, radiological, and/or biochemical findings. Genetic or serological testing is currently not recommended for routine diagnosis. As there is no single way to diagnose CD, Lennard-Jones et al. have defined macroscopic and microscopic criteria to establish the diagnosis that is currently recommended. This still results in diagnostic obstacles: a change in diagnosis to ulcerative colitis during the first year occurs in about 5% of cases [13].

After diagnosis is established, disease activity, severity, extension, and behavior should be assessed, and patients should be phenotyped to stratify their risk and to identify patients who are likely to develop severe or complicated diseases later on [2].

Prediction

Based on epidemiological, immunological , and genetic data, CD is considered to be a heterogeneous disorder with multifactorial etiology in which genetics and environment interact to manifest the disease, so it is not easy to predict. The strongest risk factor for CD is having a relative with the disease: up to 15% of CD patients report a family history of CD. If both parents are affected, the risk of developing CD is one-third [19]. However, only 13.1% of disease heritability is explained by genetic variation, highlighting the importance of epigenetic and other non-genetic environmental factors involved [2].

Therapy and Prevention

Management of CD poses an evolving challenge owing to its widely heterogenous disease presentations. Therapeutic interventions are tailored to achieve mucosal healing and deep remission which is defined as symptomatic, endoscopic, and histologic remission. Treatment choices depend on disease location, severity, and the presence of complications. For moderate to severe flares, oral or intravenous steroids are the first option. In patients with mild to moderate chronically active CD as well as in patients with steroid dependency, immunosuppressants, such as azathioprine, mercaptopurine, or methotrexate, are indicated. In the patient's refractory to steroids, monoclonal antibody against TNF-α is indicated. Other biological options are ustekinumab (monoclonal antibody against interleukin 12/23) or vedolizumab (monoclonal antibody against α4β7 integrin) with a better safety profile. Failure to medical options leads to surgical treatment. As maintenance therapy, once disease remission is achieved, immunosuppressants or biological therapies have been proven to reduce the risk of relapse during follow-up. Stricturing CD in the absence of inflammatory activity requires bowel surgery. The perianal CD must benefit from a combined medical and surgical approach, including drainage of abscesses, placement of setons, antibiotics, immunosuppressants, or biologics [20].

It is well established that CD has a preclinical period, during which dysregulated immunological pathways are evident, setting the stage for disease to manifest. Insight into this stage could offer numerous possibilities, including disease prevention, but there is no clear data regarding any intervention to identify this early stage [2].

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Celiac Disease

66

Albert Martín-Cardona and Maria Esteve

Abstract

Celiac disease is a chronic immune-mediated enteropathy triggered by gluten ingestion that affects the small bowel in genetically susceptible subjects (HLA-DQ2 and/or HLA-DQ8). This disease, occurring both in children and adults, is one of the most common disorders in Western countries. Coeliac disease is characterized by the presence of variable clinical manifestations (mainly digestive symptoms and signs of intestinal malabsorption), the presence of specific antibodies (tissue transglutaminase and endomysium), and enteropathy. At present, the only treatment for celiac disease is a strict gluten-free diet throughout life.

Keywords

Coeliac disease · HLA-DQ2 · HLA-DQ8 · Transglutaminase antibodies · Endomysium antibodies · Gluten-free diet

Description of the Disease

Celiac disease (CD) is a chronic immune-mediated enteropathy triggered by gluten ingestion (found in the following cereals: wheat, rye, barley, spelt, kamu, etc.) in genetically susceptible subjects (HLA-DQ2 and/or HLA-DQ8) [1]. CD is characterized by the presence of variable clinical manifestations (Tables 66.1, 66.2, and 66.3), the presence of specific antibodies, and enteropathy.

CD is the most frequently genetically determined chronic intestinal pathology. The prevalence of CD is influenced by the frequency of predisposing HLA haplotypes and the type and amount of cereal consumption in the general population. Therefore, the prevalence varies from one region to the other. A meta-analysis on prevalence of CD reported a global seroprevalence of 1.4% and biopsy-proven prevalence of 0.7% [1]. In a cross-sectional, population-based study performed in Catalonia (Spain) [2], we found a higher prevalence of CD in children aged 1–14 years (1:71) than in adults (1:357) with a female-male ratio of 2.5:1.

Nowadays the only effective treatment for patients with CD is a gluten-free diet (GFD) that must be strict and followed throughout life to prevent comorbidity and long-term complications such as loss of bone mineral density with a higher risk of fractures or iron deficiency anemia as the most frequent (Table 66.4). A more complete list of symptoms and complications is detailed below. Early diagnosis of CD is very beneficial, not only because patients' health improves thanks to the reversibility of symptoms with GFD, but also to avoid the associated complications.

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Signs, Symptoms of CD According to Definitions [3, 4]

Table 66.1 Forms of presentation

Classic celiac disease	More frequent in children and very rare in adults Symptoms and signs of malabsorption (diarrhea, steatorrhea, weight loss, iron deficiency anemia, growth retardation)
Non-classical celiac disease	More common in adulthood, generally monosymptomatic or oligosymptomatic Selective malabsorption of micronutrients (iron, calcium, vitamin D, etc.) is common Symptoms are gastrointestinal (abdominal pain, distention, gastroesophageal reflux, vomiting, constipation, symptoms of the irritable bowel syndrome spectrum, bloating, etc.) or extraintestinal (iron deficiency anemia, loss of bone mass, mild transaminases increase, fertility disorders)
Asymptomatic celiac disease	After a careful anamnesis, no symptoms are detected despite the fact of having a characteristic intestinal lesion. It is detected in population studies or assessment of genetically determined risk groups According to the Oslo Consensus, the term “silent,” equivalent to the term “asymptomatic,” should not be used
Subclinical celiac disease	This term is reserved for patients with symptoms or signs that have not been intense enough to initiate any research to confirm or rule it out Detected also by screening (general population or risk groups) Symptoms (e.g., fatigue) are often recognized by the improvement produced by the GFD
Potential celiac disease and latent celiac disease	Potential CD refers to patients who have a normal intestinal biopsy but with an increased risk of CD development due to the presence of certain molecular or cellular markers (positive serological tests or increase in γδ lymphocytes in the duodenum, e.g.) Latent CD has several meanings according to medical literature. It refers to patients unequivocally diagnosed with CD that have normal duodenal mucosa after gluten reintroduction or patients who in the future will have CD Potential and latent CD have been used interchangeably, but the Oslo Consensus recommends not using the “latent” term
Refractory celiac disease	Persistence or recurrence of symptoms or signs of malabsorption and intestinal villous atrophy despite a GFD for more than 12 months, after excluding other causes of villi atrophy. Divided into two types: Type I RCD: the duodenal IELs present a normal phenotype and the rearrangement of TCR genes is polyclonal Type II RCD: the duodenal IELs have an aberrant phenotype with a loss of surface markers (CD3, CD4, and CD8) and maintenance of intracytoplasmic CD3 expression. The rearrangement of TCR is oligoclonal or monoclonal

RCD refractory celiac disease, *IELs* intraepithelial lymphocytes, *TCR* T lymphocyte receptor, *GFD* gluten-free diet

Table 66.2 Clinical manifestations in patients with celiac disease [3, 5, 6]

Mode of presentation[a,b]		% in childhood	% in adulthood
Digestive symptoms and signs	– Classical symptoms[c]	62[d]	31[d]
	– Chronic or intermittent diarrhea	33[d]	18[d]
	– Symptoms of irritable bowel syndrome		6[g]
	– Persistent and unexplained gastrointestinal symptoms, including nausea or vomiting and dyspepsia		
	– Abdominal pain and/or recurrent bloating	12[d]	18[d]
	– Persistent and unexplained elevation of liver enzymes	0[d]	5[d]
Malabsorption of micronutrients	– Unexplained iron deficiency anemia or other deficiencies (vitamin B12 and folic acid)	2[d]	38[d]
	– Osteopenia/osteoporosis		20[e]
	– Osteomalacia		
	– Pathological fractures		
Specific symptoms in children/adolescents	– Growth retardation (weight and height)	16[d]	0[d]
	– Puberal retardation. Delayed menarche		
	– Anorexia		
	– Abdominal distention	4[f]	
	– Constipation	5[f]	
	– Recurrent oral thrush		
	– Hypoplasia of tooth enamel		
	– Irritability		

(continued)

Table 66.2 (continued)

Mode of presentation[a,b]		% in childhood	% in adulthood
Other symptoms and signs	– Asthenia (tired all the time)		
	– Unexplained infertility		
	– Sudden or unexpected weight loss		
	– Miscarriages and recurrent abortions		
	– Neurological disorders: ataxia and epilepsy		
	– Psychiatric disorders: Anxiety and depression		

[a] Other more frequent and/or serious diseases must be ruled out before considering that the symptoms and/or signs are secondary to CD. By consensus, symptoms must be persistent or recurring

[b] The frequency of clinical manifestations of the celiac disease depends on multiple factors: age at diagnosis (pediatric or adult), detection by symptoms, case-finding, screening of groups at risk, or screening of the general population. For that reason, we provide the percentages according to the source of information and the study design (see below)

[c] Classical symptoms include not only digestive symptoms but also signs of malabsorption such as iron deficiency anemia

[d] These are the percentages of the main symptoms or signs that induced the diagnosis of celiac disease in a series of patients referred to a tertiary hospital to confirm the diagnosis [5]

[e] These percentages correspond to the presence of this symptom in a screening for gluten-sensitive enteropathy in the working population

[f] These are the percentages of these symptoms in a cohort of children diagnosed with celiac disease in a tertiary hospital

[g] This is the percentage of this symptom in an active adult case-finding diagnosis strategy [6]

Table 66.3 Risk groups

First-degree relatives[a]	– First-degree relatives of patients diagnosed with celiac disease
Autoimmune diseases and other immunopathologies	– Type 1 diabetes mellitus – Autoimmune thyroiditis – Autoimmune hepatitis – Dermatitis herpetiformis[b] – Selective immunoglobulin A deficiency – Sjögren's syndrome – Systemic lupus erythematosus – Microscopic colitis – Juvenile chronic arthritis
Chromosomal alterations	– Down syndrome – Williams syndrome – Turner syndrome

[a] Second-degree relatives are also at higher risk of celiac disease, and therefore, a diagnostic study should be considered if they have symptoms, signs, or abnormalities related to the celiac disease spectrum

[b] It is considered the cutaneous manifestation of celiac disease

Laboratory Findings

Table 66.4 Laboratory findings and associated conditions

Iron deficiency	– Iron deficiency anemia – Angular cheilitis – Glossitis – Asthenia – Headache
Folate deficiency	– Macrocytic anemia
B12 vitamin deficiency (cobalamin)	– Peripheral neuropathy – Macrocytic anemia – Neurological disorders
Vitamin D deficiency	– Osteomalacia – Rickets
Hypocalcaemia	– Osteopenia or osteoporosis – Dental enamel defects – Hyperparathyroidism – Muscular hypotrophy tetany
Vitamin K deficiency	– Haemorrhage and ecchymosis
Elevations in transaminases	– Hepatic cytolysis
IgA deficiency	– Aphthous ulcers
Vitamin A and B deficit	– Oral mouth sores
Thrombocytopenia or thrombocytosis	– Hyposplenism
Miscellaneous (probably caused by multiple vitamin and ionic deficiencies)	– Delayed puberty – Impotence due to hypothalamic-pituitary dysfunction – Infertility (spontaneous and repeated abortions) – Preterm deliveries – Myopathy – Arthritis/arthralgia

Serological Markers

The antibodies used in the serological study of CD are described in [1, 3, 7] Table 66.5. These antibodies are very sensitive and specific for the diagnosis of CD with atrophy. However, they have a low sensitivity to the diagnosis of low-grade coeliac enteropathy, which is a common form in adulthood and practically non-existent in pediatric age.

Table 66.5 Classification of serological markers of celiac disease

Antigen	Antibody type	Sensitivity	Specificity	Definitions
Tissue transglutaminase	IgA	98 (78–100)	98 (90–100)	Serological markers of choice (ELISA technique) Due to the high sensitivity and specificity of TG2A, the ESPGHAN proposes diagnosing children and adolescents with CD without biopsy if they have IgA TG2A >10 ULN confirmed with positive EMA [7] In adulthood, a confirmatory duodenal biopsy is needed for CD diagnosis due to the high frequency of dubious diagnosis and conflicting response to a GFD
	IgG	70 (45–95)	95 (94–100)	In cases of IgA deficiency, the presence of class IgG TG2A must be determined (2.5% of patients with CD)
Endomysium	IgA	95 (86–100)	99 (97–100)	Recommended by ESPGHAN as a confirmatory serological technique if it is applied to the diagnostic protocol without duodenal biopsy (IFI technique)
	IgG	80 (70–90)	97 (95–100)	In cases of IgA deficiency
Deamidated gliadin peptide	IgA	88 (74–100)	90 (80–95)	Antibodies against DGPA are sensitive and specific but less than TG2A and exhibit different kinetics than TG2A (ELISA technique) Should not be confused with classic antigliadin antibodies which use is discouraged by ESPGHAN
	IgG	80 (70–95)	98 (95–100)	

IgA immunoglobulin A, *IgG* immunoglobulin G, *TG2A* tissue antitransglutaminase antibodies, *EMA* antiendomysis antibodies, *DGPA* antigliadin deamidated antibodies, *ESPGHAN* European Society of Paediatric Gastroenterology, Hepatology, and Nutrition, *IFI* indirect immunofluorescence, *GFD* Gluten-free diet, *ULN* upper limit normal

Genetical Markers

CD is genetically conditioned by the configuration of the HLA system (histocompatibility leukocyte antigen) (Table 66.6). The HLA-DQ2 (DQA1*05xx + DQB1*02xx) and/or HLA-DQ8 (DQA1*03 + DQB1*0302) genes encode the heterodimers DQ2 and/or DQ8 (antigen-presenting proteins) necessary for gluten to be presented to the immune system [8]. Without these genes and proteins, CD cannot develop.

Interpretation of the result of the HLA-DQ2 and/or DQ8 genetic predisposition study [8] is as follows:

- Negative genetic predisposition study: The diagnosis of CD is very unlikely (negative predictive value >99%).
- Positive genetic predisposition study: The diagnosis of CD is possible, but far from certain. To have a positive genetic predisposition study is not very specific, since 25–30% of the general population is DQ2 positive and most will not have CD. Asymptomatic patients belonging to risk groups for CD (first-degree relatives, type 1 DM, etc.), and in whom the genetic predisposition study is positive, should periodically undergo clinical and analytical controls, as they may suffer from CD in the future.

More than 90% of patients with CD are HLA-DQ2.5 positive; the remaining ones are either positive for HLA-DQ8, HLA-DQ2.2, or HLA-DQ7.5. Therefore, in patients with a negative serological test and symptoms (intestinal or extraintestinal) of the celiac spectrum, only a study with a positive result for HLA-DQ2.5 can help us make the decision to perform a diagnostic duodenal biopsy. HLA-DQ8 and HLA-DQ2.2 are useful only in the following situations:

- In the context of family studies, when the index case is positive for these genes, in order to study the rest of the family.
- To correctly interpret a pathological duodenal biopsy with celiac spectrum lesions (from Marsh I to Marsh III) when serological tests are negative. In this situation, the positivity of any of the predisposition haplotypes favors the diagnosis of CD in the presence of compatible duodenal lesions.

Table 66.6 Genetical markers in CD

			Haplotypes			
			DQB1	DQA1	DRB1	CD risk
HLA-DQ2.5 positive	HLA-DQ2.5 transmission in _cis_ (alleles from a single parent)	DR3-DQ2	HLA-_DQ B1*0201_	HLA-_DQ A1*0501_	03	Very high
	HLA-DQ2.5 transmission in _trans_ (HLA-DQ2.2 /HLA-DQ7.5) (alleles from both parents)	DR7-DQ2	HLA-_DQ B1*0202_	HLA-DQ A1*0201	07	Very high
		DR5-DQ7	HLA-DQ B1*0301	HLA-DQ _A1*0505_	11/12	
HLA-DQ8 positive (transmission always in _cis_)		DR4-DQ8	HLA-DQ B1*0302	HLA-DQ A1*0301	04	High
HLA-DQ2.2 positive		DR7-DQ2	HLA-DQ _B1*0202_	HLA-DQ A1*0201	07	Low
HLA-DQ7.5 positive		DR5-DQ7	HLA-DQB1*0301	HLA-_DQ A1*0505_	03	Low

_CD_ celiac disease, _HLA_ histocompatibility leukocyte antigen

Table 66.7 Histological classifications of gluten-sensitive enteropathy

Histological criteria			Modified Marsh's classification (Oberhuber)[a]	Corazza's classification[b]	Ensari's classification
Increased intraepithelial lymphocytes	Hyperplasia of crypts	Atrophy of the villi			
Yes	Not	Not	Type 1	Grade A	Type 1
Yes	Yes	No	Type 2		
Yes	Yes	Yes (partial)	Type 3a	Grade B1	Type 2
Yes	Yes	Yes (subtotal)	Type 3b		
Yes	Yes	Yes (total)	Type 3c	Grade B2	Type 3

[a] ≥40 intraepithelial lymphocytes per 100 enterocytes, according to the modified Marsh classification (Oberhuber)

[b] ≥25 intraepithelial lymphocytes per 100 enterocytes, according to the Corazza classification

Histologic Markers

There are different histological classifications of gluten-sensitive enteropathy, such as Marsh's classification, modified by Oberhuber, another proposed by Corazza and another by Ensari [9] (Table 66.7).

The histological study is essential in the diagnostic strategy of CD (especially in adults) and, in addition, allows to establish the severity of the lesion. Since histological lesions can have an irregular distribution, it is necessary to take several samples for intestinal biopsy (two from the bulb and four from the distal duodenum). The most widely used classification in our setting is the Marsh-Oberhuber classification, but it has been highly questioned due to the high number of categories when classifying the lesion, which makes interobserver reproducibility difficult. The Corazza classification establishes only three degrees of injury: grade A, or lymphocytic enteritis (without atrophy); grade B, or subtotal atrophy; and grade C, or total atrophy. In the most recent classification, Ensari proposes maintaining the same degrees of severity of the injury as in the Corazza classification but changes the term grade to type, to avoid the use of a term that pathologists use for tumor staging [9]. In patients with a negative serological study, the clinical and histological response to GFD is essential to reach the diagnosis of CD, since the spectrum of histopathological lesions of gluten-sensitive enteropathy is not specific to this entity. The assessment of HLA DQ2/DQ8 adds valuable complementary information.

Diagnostic Criteria

The diagnosis of CD in adults was based on the 2019 guidelines of the European Society for the Study of CD [1] and the recent Paris consensus criteria for the diagnosis of seronegative CD [10]. The diagnosis of CD in childhood was based on the ESPGHAN guidelines 2020 [7]. An anamnesis and a careful physical examination should allow a diagnosis of suspicion to be established in patients who present classic and non-classical symptoms and/or belong to risk groups. There is no histological pathognomonic lesion of CD, so diagnosis is based on the combination of clinical criteria, serological testing, histological analysis of duodenal biopsies, genetic study, and response to GFD. Under no circumstances should gluten be removed from the diet before the end of the diagnostic study. For this reason, several diagnostic criteria for CD have proposed a combination of clinical and analytical factors. One of the most accepted is the diagnostic criteria proposed by Catassi and Fasano [11] (Table 66.8).

Table 66.8 Catassi and Fasano diagnostic criteria for CD at least 4 of 5 (or 3 of 4 if the HLA-DQ2/DQ8 study is not available)

1	Typical symptoms of CD
2	CD-specific IgA class antibodies with high titters
3	Determination of HLA-DQ2 and/or DQ8[a]
4	CD compatible enteropathy in intestinal biopsy[b]
5	Response to GFD[c]

HLA histocompatibility leukocyte antigen, *CD* celiac disease, *GFD* gluten-free diet

Note: a family history of CD adds evidence to the diagnosis

[a] Positivity for HLA-DQ2 includes people with half the heterodimer (HLA-DQB1*02 positive)

[b] It includes Marsh-Oberhuber type 3 lesions, Marsh-Oberhuber type 1–2 associated with the presence of specific CD antibodies with low/high titers, or Marsh-Oberhuber type 1–3 associated with subepithelial deposits of IgA and/or increased TCR γδ+ lymphocytes

[c] Histological response is required in patients with negative serology or associated with IgA deficiency

Criticism on the Diagnostics Criteria

The most important difficulty for diagnosing CD is the wide variety of symptoms produced by the disease and its non-specificity. Additional diagnostic challenge occurs in patients with CD and negative serology. In fact, not all diagnostic criteria (symptoms, serology, genetics, etc.) have the same relevance, making positive serology the most important. For that reason, there are specific diagnostic criteria for seronegative CD, and pediatricians accept the diagnosis of CD in childhood and adolescence only with high titters of positive serology (>10 ULN) without biopsy. The diagnosis is even more difficult in patients seronegative having mild enteropathy (Marsh 1) (named "coeliac trait," "low-grade coeliac enteropathy," "coeliac-lite," or "mild enteropathy CD" among others). The ESPGHAN criteria, as well as the Catassi and Fasano criteria, make advisable the use of complementary methods in doubtful cases. Different methods that can be used are described below.

Determination of Intraepithelial Lymphocytes with T-Cell Receptor (TCR γδ+)

The subpopulation of TCR γδ+ T cells is increased in treated and untreated CD and latent or potential CD. These lymphocytes have also been detected in patients with mild enteropathy. This increase in TCR γδ+ has not been observed in other common intestinal diseases [12], and therefore, the determination may be useful for the diagnosis of gluten-sensitive enteropathy in difficult cases. The complete celiac cytometric pattern, defined by intraepithelial lymphocytes (IELs) TCR γδ+ >8.5% and CD3- <10%, has a 100% specificity for the diagnosis of CD, while the incomplete celiac cytometric pattern (IEL TCR γδ+ >8.5%, but with CD3- ≥10%) has a specificity of 91% [12, 13].

Subepithelial Deposits of IgA Antitransglutaminase Tissue

Subepithelial deposits of ATGT IgA can be detected in the intestinal mucosa and also in blood vessels [14]. Unlike the lymphocyte infiltration pattern, these antibodies are generally detected in untreated CD and discreetly improve the diagnostic performance of serological tests. Therefore, the presence of these antibodies reinforces the diagnosis of CD in doubtful cases. The technique, based on indirect immunofluorescence (IFI), is difficult to perform, and the interpretation is very subjective.

Interferon (IFN)-c-Secreting T Cells

It has been reported that interferon (IFN)-c-secreting T cells reactive to gluten can be detected in the peripheral blood of CD patients after short-term consumption of gluten-containing food (3 days). IFN-c can be transiently detected by using the enzyme-linked immune absorbent spot (ELISPOT) assays or by flow cytometry tetramer technology. The main limitations for the wide use of this technique in clinical practice are the limited sensitivity and specificity compared to available serological tests and the high cost of ELISPOT and tetramer immune assays [15]. These techniques may be useful to confirm CD in patients that have already started a GFD and do not accept prolonged gluten exposure to verify the diagnosis.

Increased Level of Serum IL-2, IL-8, and IL-10

A characteristic mucosal cytokine response has also been described in response to a short-term gluten challenge. It has been reported that a single gluten challenge in patients with CD is followed by an increased level of serum IL-2 and, to a lesser extent, IL-8 and IL-10, at 4 h thereafter [16]. This novel diagnostic method has only been used in research studies, not in routine clinical practice.

Detection of Specific Lymphocytes in Peripheral Blood

Other diagnostic techniques have been proposed to diagnose patients that have started a GFD without a conclusive diagnosis. These techniques consist of detecting (1) gut-homing CD8+ T cells in peripheral blood by flow cytometry after reintroduction of 10 g gluten/day for 3 days [17], (2) changes in plasma interleukin-2 measured 4 h after a single dose gluten challenge [18], and (3) measurement of gluten-specific CD4 T cell with HLA-DQ2-gluten tetramers after 3 g or 10 g of gluten challenge/day for 3 days [19].

Results warrant a formal comparison between the different diagnostics tests at clinical practice that could be complementary or done in a sequential manner. Further research is required to establish the appropriate diagnostic algorithm in this setting.

Can the Disease Be Predicted

Extensive research has been developed to find factors that could act as triggering CD or protecting against it. Risk factors such as age at gluten introduction, breastfeeding, cesarean delivery, infections, and exposure to antibiotics, among others, have been claimed as possible CD inducers. By contrast, others such as breast-feeding or rotavirus vaccination have been proposed as a protective, but the controversy persists [20]. Therefore, it is not possible to give firm recommendations for CD prevention.

Therapy and Prevention

At present, the only treatment for CD is strict GFD throughout life, which involves the elimination of all foods containing wheat, barley, and rye [3, 20].

It is very difficult to completely eliminate all sources of gluten, due to contamination of food by cross-traces of gluten. It has been pointed out that a diet with less than 10 mg of gluten per day is unlikely to produce alterations in most patients.

To follow a GFD correctly, natural foods such as meat, eggs, cow's milk, fish, legumes, fruits, vegetables, and gluten-free cereals, such as corn or rice, must be consumed. The persistence of symptoms after 1 year of GFD should make us think about the existence of voluntary or involuntary transgressions, and it will be necessary to review the GFD. The interview conducted by an expert nutritionist on GFD is considered one of the best indicators of this compliance, due to its low cost, being a non-invasive method, and the good correlation with the intestinal injury.

Failure to comply with GFD can lead to the persistence of short-term symptoms and long-term complications. The most serious long-term complication is intestinal lymphoma, and patients with CD have an increased risk. However, this risk remains very low. To put into context, in 1 year, 3 out of every 10,000 healthy people in the population will have lymphoma, while this will appear in 7 out of every 10,000 patients with CD. Patients with CD have a relative risk between 2 and 3 times higher than that of the general population (7/3 = 2.3) [20].

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Part VIII

Cutaneous Autoimmune Diseases

Cutaneous Lupus Erythematosus

67

Annegret Kuhn

Abstract

Cutaneous lupus erythematosus (CLE) is a rare, inflammatory autoimmune disorder that encompasses a broad spectrum of clinical manifestations. Various environmental factors influence the clinical expression of CLE, with sunlight exposure strongly linked to different subtypes of the disease. However, the complex pathophysiological mechanisms underlying CLE are still under investigation. A comprehensive patient history, histological analysis of skin biopsy specimens, photoprovocation, and serological investigations are crucial for supporting the diagnosis of CLE and providing important insights into disease activity and damage, as well as guiding appropriate therapeutic strategies. In recent years, European and German guidelines have been established by experts, outlining a diagnostic and therapeutic procedure for CLE patients.

Keywords

Autoimmune disorder · Disease activity and damage · Photosensitivity · RCLASI · Skin manifestations · Treatment

Description of the Disease

Epidemiology

Lupus erythematosus (LE) is a heterogeneous, inflammatory autoimmune disease that can involve many organs with a variable course [1]. Cutaneous lupus erythematosus (CLE) is defined as a separate disease and differentiated from systemic lupus erythematosus (SLE), although skin manifestations appear in 72–85% of patients with SLE and can occur at any stage of the disease [2]. Notably, transition from CLE to SLE has been reported for 20% of CLE patients within 3–5 years [3]. The incidence of CLE is 2–3 times higher than that of SLE, although a systematic epidemiological analysis of the various cutaneous disease subtypes has not been performed. A study from Sweden suggested that the incidence of CLE is about 4.0 per 100,000, whereas the gender ratio of females to males (3:1 to 3:2) is much lower than that of SLE (9:1) [4].

Pathogenesis

The complexity of CLE implies multifactorial aspects of the pathogenic course, including individual genetic disposition [5]. For example, there is a high association with HLA-A1, HLA-B8, and HLA-DR3 in patients with subacute cutaneous lupus erythematosus (SCLE) [6]. Additionally, subacute cutaneous lupus erythematosus (SCLE) appears to be significantly associated with a single-nucleotide polymorphism in the TNF-alpha gene promoter (−308 A), which encodes for high TNF-alpha expression [7]. The disease is simultaneously activated by the adaptive immune response (mainly autoantibodies and T cells) as well as the innate immune response with activation of apoptotic cell death, cytokines, and DAMP (damage-associated molecular pattern) pathways [8]. In addition to irritative stimuli, various drugs, and especially UV radiation, can trigger an autoimmune response against the epidermis of the different CLE subtypes [9, 10]. A significant increase of apoptotic keratinocytes has been found in primary and UV-induced skin lesions of patients with different subtypes of CLE compared with healthy controls [11]. The hypothesis that clearance of apoptotic cells in the skin of patients with CLE is either impaired or delayed is analogous to the growing evidence that defects in the clearance of apoptotic cells may be important in triggering the immune response in SLE [12].

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Table 67.1 Düsseldorf classification of cutaneous lupus erythematosus 2004 (modified after [13])

Acute cutaneous lupus erythematosus (ACLE)
Subacute cutaneous lupus erythematosus (SCLE)
Chronic cutaneous lupus erythematosus (CCLE)
Discoid lupus erythematosus (DLE)
Lupus erythematosus profundus (LEP)
Chilblain lupus erythematosus (CHLE)
Intermittent cutaneous lupus erythematosus (ICLE)
Lupus erythematosus tumidus (LET)

Classification

The clinical presentation of CLE shows significant variability, resulting in the classification of four different subtypes of the disease [2]. According to the 2004 Düsseldorf Classification, these subtypes are based on combinations of clinical manifestations, histological findings, laboratory results, and the average duration of skin lesions: acute CLE (ACLE), subacute CLE (SCLE), chronic CLE (CCLE), and intermittent CLE (ICLE) (Table 67.1) [13]. The CLE subtypes exhibit LE-specific histopathological changes and may be associated with SLE to varying degrees. In contrast, skin lesions such as urticarial vasculitis and livedo reticularis are among the most common LE-nonspecific cutaneous manifestations and are frequently associated with SLE, indicating potential serious complications.

In 2019, the ACR criteria (American College of Rheumatology, established in 1982, revised in 1997) and the SCLICC criteria (Systemic Lupus Erythematosus Collaborating Clinics Group, established in 2012) were replaced by a new scoring system for the classification of SLE developed by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) [14]. This change originated from the observation that a significant number of SLE patients met the previous ACR and SLICC criteria for SLE without necessarily exhibiting systemic (organ) involvement. The new criteria include additional specific skin manifestations and are designed to better differentiate between CLE and SLE.

Diagnostic Criteria

Clinical Manifestations

ACLE typically occurs in association with systemic manifestations, often preceding the onset of a multisystem disease by weeks or months. Sun exposure is a common external factor capable of triggering ACLE, with up to 82.2% of patients reporting exacerbation of systemic symptoms after sunlight exposure [2]. Additionally, infections, particularly viral infections, or certain drugs, like hydralazine, isoniazid, and TNF-alpha antagonists, have been found to induce or worsen this condition. Localized ACLE commonly presents as the classic “malar rash” or “butterfly rash” in the central portion of the face, sometimes transiently affecting the skin before the onset of a multisystem disease. The cutaneous lesions typically start as symmetric, small, discrete erythematous macules and papules on the cheeks and nose, occasionally accompanied by fine scales that gradually merge into a larger plaque. Lesions of localized ACLE on the face such as edema may be severe in some patients and have also been observed in 15% of patients with SCLE. Generalized ACLE is less common and usually coincides with exacerbation of systemic organ manifestations and prolonged disease activity. This form is characterized by a widespread, symmetrically distributed, maculopapular erythematous rash, sometimes accompanied by itching, with a focus on the areas exposed to UV light. The involvement of hands and feet is common, while the knuckles are typically spared. Skin lesions of generalized ACLE may resemble a drug eruption or, in rare cases, mimic toxic epidermal necrolysis (TEN-like ACLE). Superficial ulceration of the oral or nasal mucosa is common in ACLE, with the hard palate being the most affected area, although the labial, gingival, buccal, and lingual mucosa may also be involved. ACLE skin lesions usually heal without scarring.

SCLE is a distinct entity with specific clinical and serological features, often associated with a characteristic immunogenetic background, including the 8.1 ancestral haplotype, a common Caucasoid haplotype carried by most individuals who type for HLA-B8 and HLA-DR3. This subtype is characterized by the production of anti-Ro/SSA antibodies and can be triggered by UV light as well as by several different drugs, such as thiazide diuretics, calcium channel blockers, ACE inhibitors, and allylamine antifungals [6]. The characteristic skin lesions of SCLE typically appear symmetrically distributed on sun-exposed areas (e.g., extensor areas of the upper extremities, V area of the neck, shoulders, trunk, and, less commonly, the face). Initially, skin lesions of SCLE present as erythematous macules or papules that may evolve into scaly, papulosquamous, or annular/polycyclic plaques. Approximately 50% of patients exhibit predominantly papulosquamous or psoriasiform lesions, while the other half display the annular/polycyclic variant; few patients develop a mixed form with both types of lesions. Individual annular lesions can expand, merge with polycyclic confluence, and demonstrate central hypopigmentation. As a characteristic feature of the disease, SCLE can resolve with vitiligo-like hypopigmentation but does not lead to scarring as seen in DLE. Vesicles may arise at the active margins of the lesions, and a severe manifestation known as TEN-like SCLE can develop. SCLE may present with mild systemic symptoms, such as arthralgia and myalgia, but no more than 10–15% of patients experience complications of SLE over their lifetime.

Discoid LE (DLE) is the most common subtype of CCLE and can manifest as localized DLE (80%) with lesions above the neck or as disseminated DLE (20%) with lesions both above and below the neck. The disseminated form, especially when involving the trunk, is associated with an increased risk of progression to SLE [15]. Antinuclear antibodies (ANAs) in low titers are detected in 30–40% of DLE patients; however, less than 5% exhibit high ANA titers as seen in SLE. Anti-Ro/SSA antibodies are only occasionally found in DLE patients [4]. The first morphological sign of DLE is a well-defined, coin-shaped (discoid) erythematous patch of varying size followed by follicular hyperkeratosis, which adheres to the skin. Upon removal of the adherent scale, follicle-sized keratotic spikes similar to carpet tacks can be observed (the "carpet tack sign"). DLE lesions slowly expand with active inflammation and hyperpigmentation at the periphery, leaving depressed central atrophy and scarring, telangiectasia, and hypopigmentation. The central atrophic scarring is highly characteristic of this subtype. Primarily, the lesions occur in UV-exposed areas such as the scalp, face, ears, neck, and arms but may also be found on the palms, soles, and in inguinal folds. On the scalp, DLE can progress to total, irreversible scarring alopecia. Mucous membrane involvement is present in approximately 25% of DLE patients but does not necessarily indicate systemic manifestation or high disease activity. The buccal mucosa is most commonly involved, with discoid plaques exhibiting erythema, radiating white striae, and telangiectasia. Additionally, DLE can develop following any form of skin trauma (Koebner's phenomenon or isomorphic response).

Further subtypes of CCLE include LE profundus/panniculitis (LEP) and chilblain LE (CHLE). LEP is characterized by indurated nodules or plaques resulting in deep lipoatrophy, while CHLE is characterized by purple, painful plaques in cold-exposed acral areas, mostly on the toes and fingers, which may become hyperkeratotic and ulcerate.

Lupus erythematosus tumidus (LET) has been defined as a distinct entity of CLE in the 2004 Düsseldorf classification, named intermittent cutaneous LE (ICLE) [13]. In several regards, LET differs from other variants of CLE. Scarring, the hallmark of DLE, does not occur in LET, even in patients with recurrent skin lesions. Anti-Ro/SSA and anti-La/SSB antibodies have been found in about 10% of patients with LET, and association with systemic disease seems to be very rare in patients with this subtype. Clinically, LET is characterized by succulent, urticaria-like, single or multiple plaques with a bright, reddish, or violaceous smooth surface. The swollen appearance of the lesions and the absence of clinically visible epidermal involvement are the most important features of LET [16, 17]. The borders are sharply limited, and in some cases, there is a tendency for the lesions to coalesce in the periphery, producing a gyrate configuration, or to swell in the periphery and flatten in the center. The skin lesions of patients with LET are primarily found on sun-exposed areas, such as the face, upper back, V area of the neck, and extensor aspects of the arms; phototesting has confirmed that patients with LET are more photosensitive than those with other subtypes of CLE.

Histology

To confirm the diagnosis of CLE, histological examination of skin biopsy specimens is recommended in correlation with clinical evaluation of the lesions (except in cases of ACLE if SLE has already been confirmed). The different subtypes of CLE often show similar histological features with superficial and deep perivascular and periadnexal lymphocytic infiltrate as well as the so-called "interface-dermatitis," a lymphocytic infiltrate of the dermoepidermal junction. Characteristics include the vacuolization of basal keratinocytes and colloid bodies, as well as the thickening of the basement membrane as a late consequence [18, 19]. Histological criteria may support the clinical diagnosis of the different CLE subtypes, such as acanthosis and mucin deposition, which may vary depending on the disease subtype. For example, histological findings are usually less prominent in ACLE relative to the impressive clinical picture. In fully developed DLE lesions, there is prominent ortho- and parakeratosis, follicular plugging, and epidermal atrophy. SCLE lesions generally have less hyperkeratosis and follicular plugging compared to DLE. The periappendageal inflammation that is characteristic of DLE is less prominent in SCLE and ACLE. Lobular lymphocytic panniculitis is characteristic of LEP; however, the absence of the characteristic epidermal and dermal changes of CLE can make the histological diagnosis sometimes challenging when there is no overlying DLE. Abundant mucin deposition between collagen bundles is characteristic of LET, and usually, there is no sign of epidermal involvement or vacuolar degeneration of the dermoepidermal junction.

Direct Immunofluorescence

Direct immunofluorescence (DIF) can be performed on skin biopsy specimens of patients with CLE, detecting lesional granular deposits of C3 at the dermoepidermal junction as well as the immunoglobulins IgG, IgM, and, in rare cases, IgA [19]. However, the number of positive results varies greatly among different studies [4]. This might be due to controversies concerning the terminology of DIF. Some groups use the term "lupus band test" (LBT) to refer to lesional and non-lesional DIF findings in CLE and/or SLE, whereas others reserve this designation for immunofluorescence examination of non-lesional skin of SLE only. The strongest clinical association of positive DIF in non-lesional, sun-protected skin has been with SLE, and patients with DLE without clinical or laboratory evidence of extracutaneous disease have been uniformly negative. Furthermore, DIF findings at the dermoepidermal junction are not specific for CLE, because similar deposits can also be found in normal or sun-damaged skin, especially in the face, and in other non-LE dermatological conditions [20].

Photoprovocation

Due to the clinical evidence demonstrating the clear relationship between sunlight exposure and skin manifestations of CLE, photoprovocation with different wavelengths has been developed to better define UV sensitivity in patients with a photosensitive subtype of CLE [21]. Photoprovocation can be carried out by irradiating defined test areas with single doses of 60–100 J/cm^2 UVA and/or 1.5 MED UVB daily for three consecutive days using a standardized protocol (Table 67.2). There are substantial differences in the clinical subtypes of CLE with regard to responses to the different UV wavelengths. Patients with LET have been found to be the most photosensitive subtype of CLE, as phototesting revealed characteristic skin lesions in 72% of the patients. In contrast, pathological skin reactions were induced by UV irradiation in 63% of patients with SCLE, in 60% of patients with ACLE, and in 45% of patients with DLE [22]. Most importantly, the specific CLE lesions will only appear after a latency of 8 ± 4.6 days after UV exposure and will then persist for some weeks. In contrast, other photodermatoses such as polymorphous light eruption (PLE) will appear much earlier after UV exposure, and the lesions will subsequently resolve.

Table 67.2 Protocol of phototesting in patients with cutaneous lupus erythematosus (modified after [24])

Test site	Non-UV exposed, unaffected areas of the upper back or extensor aspects of the arm
Size of test field	Defined test areas that should be sufficiently
Dosage	Large to provide reactions (e.g. 4 × 5 cm) 60–100 J/cm^2 UVA and/or 1.5 MED UVB on three consecutive days
Light sources	UVA: UVASUN 3000 (330–460 nm), Waldmann; or UVA1 Sellamed 2000 (340–440 nm), (Sellas Medizinische Geräte, Gavelsberg, Germany) UVB: UV-800 with fluorescent bulbs, Philipps TL 20 W/12 (285–350 nm), (Waldmann, Villingen/Schwenningen, Germany)
Evaluation	24, 48, and 72 h up to 4 weeks after irradiation
Criteria for positive photoprovocation	– Induced skin lesions clinically resemble CLE – Skin lesions develop slowly over several days or weeks – Skin lesions persist for up to several months – Histopathological analysis confirms clinical diagnosis

Laboratory Parameters

Laboratory investigations are crucial for primary screening tests to confirm or exclude the diagnosis of CLE and to effectively rule out systemic organ manifestations [23]. This is particularly important for patients with ACLE (most frequently associated with SLE) and/or in patients with SCLE (frequently associated with arthritis or other moderate organ involvement). Moreover, laboratory investigations are important not only for assessing the activity and prognosis of the disease but also for monitoring drug side effects. The frequency of laboratory investigations depends on individual factors such as the severity and activity of the cutaneous disease, treatment, comorbidities, and previous findings (such as the detection of ANA or ENA) and changes in laboratory values (such as anti-dsDNA antibodies or complement). High titers of ANA and the detection of anti-dsDNA antibodies should raise suspicion of SLE and can also be markers for the transition from CLE to SLE. Moreover, determining hemolytic complement activity (CH50) should be reserved for individual cases of CLE with a high suspicion of systemic disease or associated hypocomplementemic urticarial vasculitis. In these cases, C1q and anti-C1q antibodies should also be measured.

The clinical, histological, and laboratory signs and symptoms, as well as the prognosis of the four different subtypes of CLE, are summarized in Table 67.3, simplifying and grading the specific characteristics. In Table 67.4, the differential diagnoses of the different CLE subtypes are listed, including the rare variants LEP and CHLE.

Organ-Specific Diagnostics and Interdisciplinary Investigations

In case of abnormalities in laboratory investigations, further diagnostic steps such as X-rays, MRI, echocardiography, or ultrasound must be initiated to define any potential systemic organ manifestations. The musculoskeletal, hematological, renal, cardiopulmonary, and neurological systems need to be monitored in case of clinical symptoms due to various risk factors in SLE patients [23].

Table 67.3 Signs and symptoms of the different subtypes of cutaneous lupus erythematosus (modified after [24])

CLE subtype	ACLE	SCLE	DLE	LET
Clinical presentation				
Edema/induration	+	(+)	++	+++
Desquamation	+	++	++	0
Hypopigmentation	0	+++	++	0
Hyperpigmentation	0	0	++	0
Follicular hyperkeratosis	0	0	+++	0
Scarring	0	0	+++	0
Photosensitivity	++	+++	+	+++
Histopathology				
Orthohyperkeratosis	0	(+)	++	0
Interface dermatitis	+	++	++	0
Thickened basement membrane	+	++	+++	0
Lymphocytic infiltrate	+	++	+++	+++
Interstitial mucin deposition	+	++(+)	++	+++
Direct immunofluorescence (DIF)				
Lesional skin	+++	++	+++	+
Non-lesional, sun-protected skin	++(+)	(+)	0	n.d.
Serology (autoantibodies)				
ANA (HEp-2 cells)	+++	++	+	+
Anti-dsDNA	+++	0	0	0
Anti-Sm	++	0	0	0
Anti-Ro/SSA	+	+++	0	+
Anti-La/SSB	+	++(+)	0	+
Prognosis/risk for SLE	+++	+	(+)	0-(+)

Table 67.4 Differential diagnosis of cutaneous lupus erythematosus (modified after [23])

ACLE
– Localized: dermatomyositis, rosacea, seborrheic eczema, tinea faciei, perioral dermatitis, syphilis II
– Generalized: viral or drug-induced exanthema, erythema multiforme, toxic epidermal necrolysis (TEN)
SCLE
Psoriasis vulgaris, tinea corporis, mycosis fungoides, erythema multiforme/toxic epidermal necrolysis (TEN), erythema annulare centrifugum (EAC), erythema gyratum repens, drug rash, nummular eczema, seborrheic eczema
DLE
Tinea faciei, lupus vulgaris, sarcoidosis, actinic keratosis
LEP
Panniculitis, subcutaneous sarcoidosis, polyarteritis nodosa, morphea profunda, subcutaneous granuloma annulare malignant lymphoma (especially subcutaneous panniculitis-like T-cell lymphoma)
CHLE
Perniones (chilblains), lupus pernio (chronic form of skin sarcoidosis on the acra), acral vasculitis/vasculopathy
LET
Jessner lymphocytic infiltration (JLIS)/palpable migratory arciform erythema, polymorphic light eruption, pseudolymphoma, B-cell lymphoma, plaque-like cutaneous mucinosis, solar urticaria

Disease Area and Severity Index

Several scoring systems have been developed for patients with SLE to determine disease activity, such as ECLAM (European Consensus Lupus Activity Measurement), BILAG (British Isles Lupus Assessment Group), SLAM (Systemic Lupus Activity Measure), or SELENA-SLEDAI (Systemic Lupus Erythematosus Disease Activity Index). Although these scores include dermatological criteria, such as rash, generalized erythema, and oral ulcers, they are not suitable for evaluating the activity of different CLE subtypes. For this reason, the scoring system CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index) was developed for CLE patients in 2005 and revised in 2010, taking into account both anatomical regions (e.g., face, chest, arms) and morphological aspects (e.g., erythema, scale/hypertrophy, edema/infiltration, dyspigmentation, scarring) of skin lesions [25, 26]. Furthermore, the RCLASI (Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index) allows for separate assessment of the “activity” and “damage” of the disease, with scores ranging from 0 to 3 points assigned to each lesion. Alopecia is evaluated using a separate scoring system, distinguishing between non-scarring (0–3 points) and scarring (0–6 points) forms. The validity and practicality of the CLASI and the RCLASI have been confirmed in reliability analyses and can be used not only to evaluate disease activity for therapeutic response and treatment monitoring but also to support the diagnosis of various CLE subtypes [23].

Prevention and Treatment

According to the European Guidelines on CLE, guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV) [27], preventive measures are very important to protect against the development of skin lesions and the worsening of the disease, particularly with regard to the transition to SLE. Most importantly, protection from sunlight and artificial sources of UV irradiation and avoidance of potentially photosensitizing drugs are necessary [28]. Sun exposure should be avoided especially around noon (11 a.m.–3 p.m.), and patients should be warned that clear glass (including car windows) does not protect against UV-A radiation. Apart from sun-protective clothing and broad-brimmed hats, sunscreens with chemical and/or mineral UV-A and UV-B filters are essential. These should be applied in sufficient quantity (about 2 mg/cm^2) 20–30 min before sun exposure [29]. A prospective, randomized, double-blind, intra-individual, vehicle-controlled study demonstrated the prevention of CLE skin lesions during photoprovocation in 16 patients after the application of a broad-spectrum sunscreen with chemical and mineral UV-A/UV-B filter and vitamin E added as an antioxidant [30].

Current therapeutic strategies for CLE have limitations, as neither topical nor systemic medications have been specifially approved for this disease. The current treatment is based on a small number of randomized controlled trials; however, recommendations for treating patients with CLE are based on the European S2k guideline from 2017, which also includes an algorithm [27]. This algorithm covers first-line, second-line, and third-line treatment options, which were modified within the framework of the current German S2k guideline, published in 2021 [23]. Topical corticosteroids show efficacy in the treatment of patients with all different subtypes of localized CLE; however, they are of limited value in the treatment of widespread skin lesions due to the well-known side effects, such as atrophy, dyspigmentation, and telangiectasia. A randomized, controlled trial showed that tacrolimus 0.1% ointment was significantly more effective in CLE patients with different subtypes of CLE than a placebo cream [30]. Tacrolimus 0.1% ointment was most effective in patients with LET, followed by SCLE patients. Facial lesions responded better than lesions on the body, especially when the lesions had been present for <6 months. Therefore, topical calcineurin inhibitors are now recommended as first-line treatment in CLE predominantly for treating facial lesions but also as an alternative to topical corticosteroids. For widespread skin lesions, an inclination to scarring, or insufficient response, in combination with systemic treatment is recommended [27].

The mainstay of treatment for widespread or localized disfiguring skin manifestations in patients with CLE, irrespective of the subtype of the disease, is antimalarial agents (hydroxychloroquine, chloroquine, and mepacrine). Additional treatment options, such as methotrexate, dapsone, and retinoids, are beneficial for patients with resistant disease; however, side effects must be considered [23]. Advances in biotechnology have led to the development and approval of novel systemic agents for treating SLE, such as belimumab and anifrolumab [32, 33]. Both drugs are also effective in the treatment of CLE, and ongoing randomized controlled trials are investigating their efficacy on the different subtypes of the disease. Some promising drugs, like baricitinib [21], have not gained approval for SLE, while others, like tofacitinib, have even induced CLE [34]. Currently, several phase 2 and 3 clinical trials are being performed in CLE and SLE, using skin-specific outcome measures, targeting, for instance, type I interferon, its downstream signaling, and plasmacytoid dendritic cells [35]. Nevertheless, further translational research and clinical trials are important for developing effective therapies in CLE, due to the persistently high unmet need for patients with the autoimmune disease.

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68

Pemphigus and Bullous Pemphigoid

Daniel Mimouni and Meital Oren-Shabtai

Abstract

Pemphigus and bullous pemphigoid are organ-specific autoimmune disorders with an established immunological basis but unknown etiology. Pemphigus has three variants categorized by the presence/absence of intraepithelial blisters and erosions of the skin and variable involvement of the mucous membranes. The diagnosis of pemphigus and bullous pemphigoid is based on the clinical picture and confirmed by distinct immunopathological findings. In general, the natural history of pemphigus is characterized by constant progression with a high mortality risk; the prognosis of bullous pemphigoid is more favorable. There are no prognostic indexes for the different variations of the diseases. Treatment consists of systemic corticosteroids, corticosteroid-sparing agents, and specific immunobiological agents. Bullous pemphigoid tends to be more responsive to treatment and may also respond to topical as well as anti-inflammatory agents.

Keywords

Autoimmune bullous diseases · Pemphigus · Pemphigoid
Desmogleins

Definition

Pemphigus and bullous pemphigoid (BP) are autoimmune blistering diseases with an established immunological basis but unknown etiology. Pemphigus is characterized by a loss of cell–cell adhesion (acantholysis) mediated by autoantibodies to epidermal cell surface proteins [1]. There are three major variants: pemphigus vulgaris (PV), pemphigus foliaceus, and paraneoplastic pemphigus, differentiated by the presence/absence of flaccid (intraepithelial) blisters and erosions of the skin and variable involvement of the mucous membranes. BP is characterized by tense (subepidermal) bullae, in vivo deposition of autoantibodies and complement components, and significant eosinophilic cell infiltrates along the epidermal basement membrane zone [2].

Epidemiology

The general incidence of pemphigus is approximately 1 per 100,000 population. PV is the most common variant of pemphigus with an estimated incidence of 0.1–0.5 per 100,000 population. Mean age of onset is 50–60 years; sex distribution is equal. The disease affects members of all races, although epidemiologic data suggest a wide geographic variability, with higher rates in Jews of northern European origin [3].

BP is the most common autoimmune blistering skin disease, affecting mainly individuals in the eighth decade of life. A notable trend of increasing incidence has been reported, probably related to the growing life expectancy, with current estimates ranging from 6 to 20 per million population annually. There has been a rise in rates of BP induced or associated with the use of various systemic drugs, mainly diuretics, antidiabetics, and PD-1 inhibitors [4, 5].

Pathogenesis

Pemphigus is caused by autoantibodies against structural components that maintain cell–cell adhesion in the skin and mucous membranes, termed desmogleins, which are part of the cadherin molecule family [1]. Desmoglein 1 (molecular weight 165 kDa), expressed in the superficial upper layers of the skin epidermis, is the target antigen in pemphigus foliaceus. Desmoglein 3 (molecular weight 130 kDa), expressed in the basal lower layers of the epidermis and more promi-

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nently on mucosal surfaces than desmoglein 1, is the target antigen in PV [6]. There is solid evidence that pemphigus autoantibodies are pathogenic and not just surrogate markers of the disease. They are invariably found in serum and bound in lesional epithelia; the severity of pemphigus correlates with the serum autoantibody titer. Transplacental transfer of pemphigus antibodies may induce a short-term blistering eruption in neonates, and passive transfer of human pemphigus antibodies to mice produces acantholysis and intraepidermal detachment, reproducing the human disease [7].

The pathogenesis of BP involves circulating autoantibodies against the hemidesmosomal proteins BP antigen 1 (230 kD) and BP antigen 2 (180 kD) also known as type XVII collagen. These antigens are key components of the epidermal hemidesmosomes, which are adhesion structures that anchor the epidermal basal cells to the underlying basement membrane [8].

Clinical Manifestations

Table 68.1 compares the main characteristics of the two autoimmune bullous diseases. In PV, the lesions typically occur first in the oropharyngeal mucosa and subsequently in the skin. Other mucosa such as the genitalia and conjunctiva may be involved as well. The primary skin lesions consist of flaccid vesicles or bullae that easily rupture and form large painful erosions that usually fail to heal without specific intervention (Fig. 68.1a–c). The most common sites are the scalp, face, and trunk, although all parts of the body may be affected. The lesions heal with crusts with gradual re-epithelization and may leave a residual postinflammatory hyperpigmentation, without a scar. Pemphigus foliaceus is characterized solely by cutaneous lesions, without involvement of mucous membranes. The blisters form superficially in the upper epidermis. They are highly fragile and easily

Table 68.1 Comparison of the main characteristics of cutaneous autoimmune bullous diseases

Characteristic	Pemphigus vulgaris	Bullous pemphigoid
Age of onset	30–50 years (middle age)	>60 years (elderly)
Sex	Equal distribution	Equal distribution
Main symptom	Pain and discomfort Low intake leading to weight loss	Severe pruritus
Nikolsky sign	Positive	Negative
Typical lesions	Flaccid, easily ruptured vesicles leading to erosions	Polymorphic eruption; may be preceded by a pre-bullous phase (erythematous urticarial papules and plaques) Tense blisters filled with clear or hemorrhagic fluid superimposed on inflamed or normal-appearing skin
Mucosal involvement	Common	Rare
Oral	70–90% [9]	10–20% [10]
Naso-laryngeal	50–75% [11]	Extremely rare
Genital	20–50% [12]	
Conjunctival	15–25% [13]	

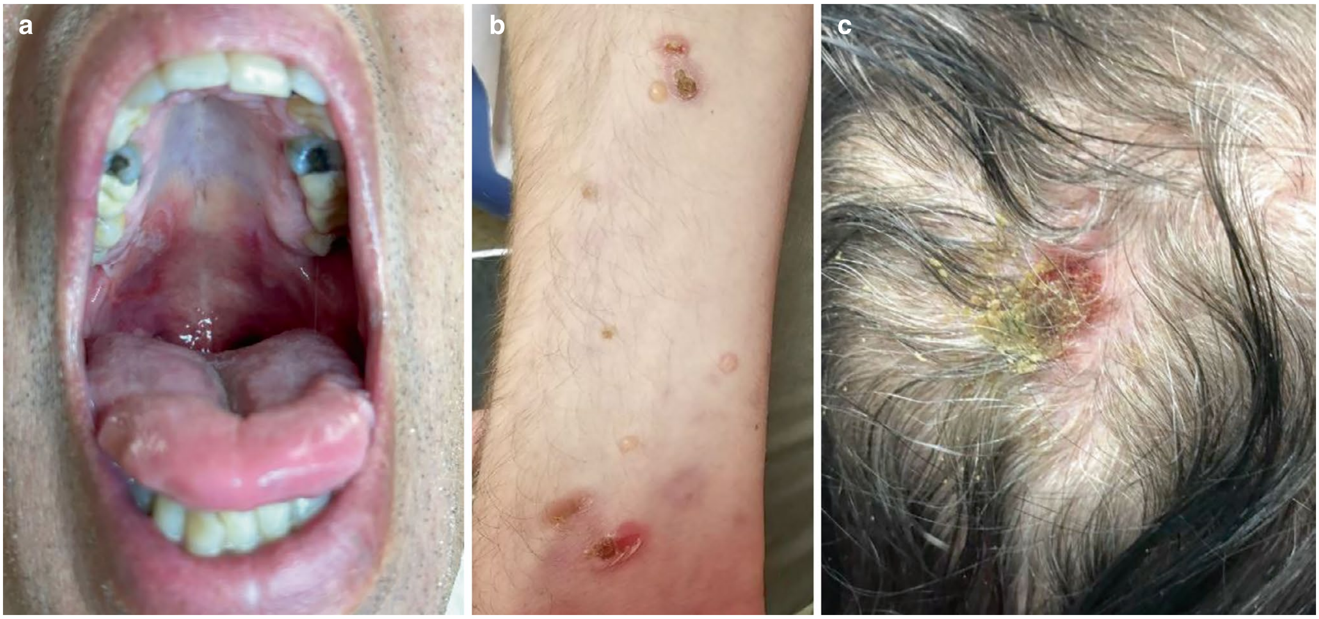

Fig. 68.1 Mucocutaneous findings in pemphigus vulgaris. Bilateral erosions on the soft palate (**a**) flaccid vesicles and crusted erosions on the forearm (**b**) and scaly-crusted large erosion on the scalp (**c**)

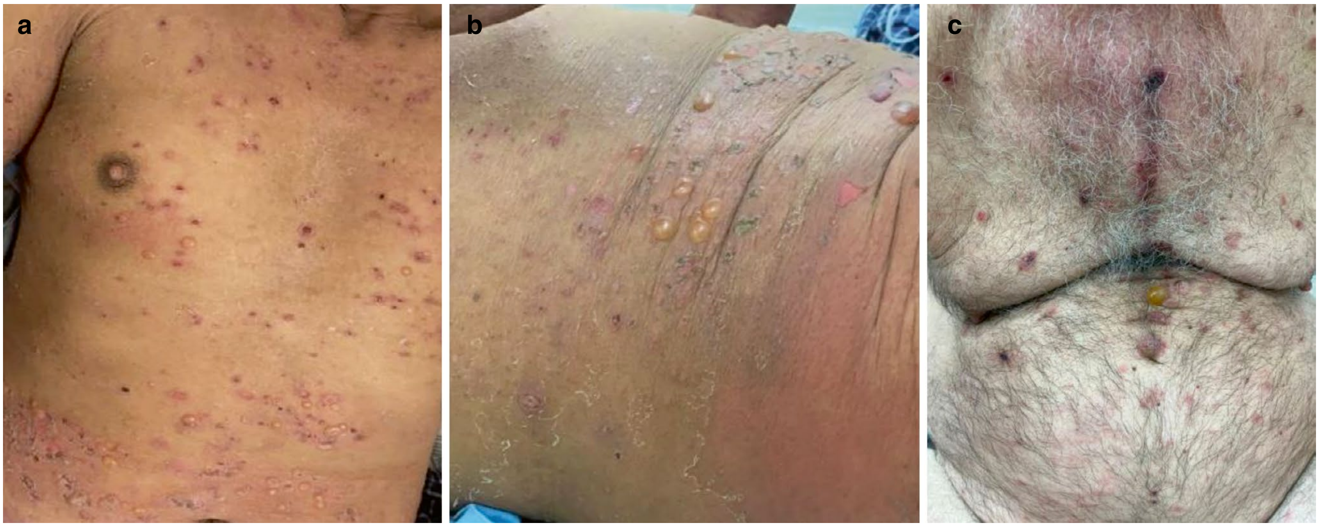

Fig. 68.2 Cutaneous findings in bullous pemphigoid. Tense bullae superimposed on an erythematous skin, accompanied by hemorrhagic-crusted erosions on the torso of two elderly bullous pemphigoid patients (**a**–**c**). Confluent inflamed urticarial plaque (**b**)

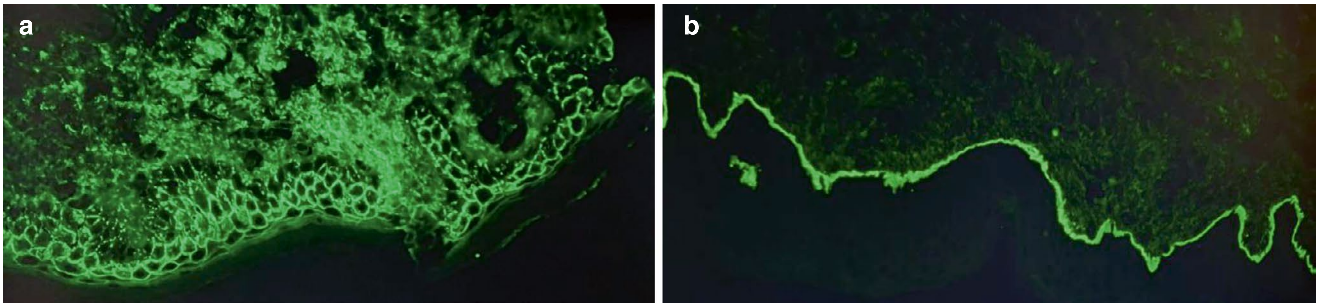

Fig. 68.3 Direct immunofluorescence patterns. Pemphigus vulgaris showing intercellular IgG deposition (**a**) and bullous pemphigoid demonstrating a linear IgG linkage along the basement membrane zone (**b**)

rupture, leaving scaly or crusted erosions. Nikolsky sign, i.e., intraepidermal separation induced by application of friction to non-lesional skin which leads to de novo erosion/blister formation, is typically positive in active PV [6].

BP differs clinically from PV. Mucosal lesions are present in only 10–20% of cases, and the skin lesions are typically polymorphic, causing severe pruritus. Patients may primarily present with a prodromal phase consisting of erythematous urticarial papules and plaques on the trunk and flexor aspects of the extremities. Subsequently, tense hemorrhagic blisters arise on either normal or erythematous skin (Fig. 68.2a–c), sometimes producing an extensive bullous eruption. Nikolsky sign is typically negative in BP [4, 14].

Laboratory Findings

Pathological Features

In both PV and BP, a histological sample should be obtained from a recent intact vesicle or bulla. If the lesion cannot be sampled in its entirety, a sample should be taken from the border. PV lesions typically show suprabasilar acantholysis, with basal keratinocytes appearing as a “row of tombstones.” BP lesions typically show separation of the basal epidermis from the adjacent dermis (subepidermal plane) with eosinophilic epidermal and dermal infiltrates [1, 2].

Immunofluorescence and Serological Features

Direct immunofluorescence (DIF) testing of non-lesional skin tissue adjacent to a PV lesion shows the deposition of IgG with or without C3 on the epithelial cell surface (Fig. 68.3a). The immunoserological hallmark of PV is the presence of serum anti-desmoglein 1 and 3 autoantibodies. This may be confirmed by indirect immunofluorescence (IIF) assay showing intercellular IgG linkage on monkey esophagus substrate.

By contrast, in DIF study of tissue from patients with BP, IgG and C3 are deposited continuously along the basement membrane (Fig. 68.3b). The immunoserological hallmark of

BP is the presence of autoantibodies against serum BP-1 and BP-2 antigens. IIF assay shows IgG and C3 linkage to the dermoepidermal junction of the monkey esophagus substrate.

Other, nonroutine, serological tests that can detect anti-desmoglein and anti-BP antibodies with more accuracy include ELISA and immunoblotting [15].

Diagnostic Criteria

At present, there are no universally recognized diagnostic criteria for PV or BP. Nevertheless, expert panels from several European countries recently developed international diagnostic and management guidelines [16, 17]. Table 68.2 summarizes the main accepted criteria for the diagnosis of PV and BP. The diagnosis of pemphigus requires a clinical presentation and histopathology findings that are consistent with the disease and either a positive DIF microscopy study or serologic detection of autoantibodies against epithelial cell surface antigens [16]. The diagnosis of BP, in most cases, relies on suggestive clinical and/or histological features, a positive DIF study, and the presence of serum IgG antibodies [17]. We strongly suggest that in both diseases, but especially pemphigus, a confirmatory DIF assay should serve as an essential, even mandatory, step in the diagnosis. The sensitivity of a mucosal DIF biopsy for the diagnosis of PV is 89%, and the specificity is 99%. For BP, the sensitivity is 68%, which is reasonably high considering the lack of mucosal involvement [18], and the specificity is 98%, similar to that for PV.

Prognosis

PV has a chronic course with remissions and flares. Left untreated, it progresses steadily and is associated with a very high risk of mortality. The introduction of corticosteroids, and, later, advanced therapies, has rendered the disease treatable but not definitively curable [16].

The course and prognosis of BP are more favorable. There are also remissions (sometimes spontaneous) and flares, but symptoms frequently disappear after a few months to a few years. BP is associated with significant morbidity and severely impaired quality of life. One-year mortality is two to three times higher for patients with BP than for age- and sex-matched controls [4].

There are at present no definitive prognostic indices for the variations of the diseases.

Therapy

In both PV and BP, the aim of therapy is to promote the healing of existing lesions and prevent the development of new ones. If PV is not treated definitively and promptly, the process "hardens," leading to epitope spreading which makes the disease more difficult to control. Even if the initial presentation is limited, the disease will be generalized without systemic treatment. Initially, systemic corticosteroids are administered at a dose equal to prednisone 0.5–1.5 mg/kg/day, usually with an anti-CD20 monoclonal antibody (rituximab). The use of rituximab has utterly changed the prognosis and course of this fatal disease. An

Table 68.2 Diagnosis of autoimmune bullous diseases

Criteria	Pemphigus vulgaris[a]		Bullous pemphigoid[b]	
Clinical presentation	*Major*	Flaccid blisters and painful erosions in mucosa, skin, or both	*Major*	Pruritic polymorphic eruption with tense blisters and erosions on inflamed or normal skin (rarely mucosa); may be preceded by a pre-bullous prodromal phase
Histopathology		Intraepidermal blisters with suprabasal acantholysis		Subepidermal blistering with epidermal and dermal eosinophils
DIF (perilesional skin)	*Minor*	Intercellular IgG and/or C3 deposition on epithelial cell surface		Linear IgG and C3 deposition along the basement membrane
IIF (monkey esophagus substrate)		Intercellular deposition of IgG and C3 on epithelial cell surface	*Minor*	Linear IgG and C3 deposition along the basement membrane
ELISA		Desmoglein 1 or 3		BP antigen 1 or 2
Immunoblot[c]		Band at 130 or 160 kDa		Band at 180 or 230 kDa

DIF direct immunofluorescence, *IIF* indirect immunofluorescence, *ELISA* enzyme-linked immunosorbent assay

[a] The definitive diagnosis of pemphigus vulgaris requires two major and one minor positive criteria [16]

[b] The definitive diagnosis of bullous pemphigoid requires three major criteria or two major (one of which is a positive DIF) and one minor criteria [17]

[c] In cases of an atypical presentation or a differential diagnosis of another autoimmune bullous disease, immunoblot may be performed

adjuvant immunosuppressive agent may be administered to allow for corticosteroid tapering and to reduce the significant steroidal side effects. First-line corticosteroid-sparing agents are azathioprine and mycophenolate mofetil. Other options with relatively high efficacy are intravenous immunoglobulins (IVIG), immunoadsorption, and cyclophosphamide [16, 19].

BP is more responsive to treatment than PV. Primarily, a thorough drug history should be obtained to identify any associated drug and consider its cessation. The therapeutic regimen, like for PV, is based on topical or systemic corticosteroids. Topical lesion-targeted application may be sufficient in mild-moderate localized disease. In nonlocalized disease, whole-body application of a super-potent topical corticosteroid once or twice a day was found to be as efficient as systemic steroid administration [20]. Moderate widespread disease may necessitate systemic administration of oral prednisolone, 0.5 mg/kg/day, either alone or in conjunction with other immunosuppressive drugs. Possible adjuvant therapies are doxycycline, dapsone, methotrexate, azathioprine, cyclosporine, and mycophenolate mofetil. Other treatments, such as plasmapheresis and high-dose IVIG, are optional in cases of resistant BP. Recently, reports on novel targeted therapies (rituximab, omalizumab, dupilumab) have been accumulating, showing promising efficacy with good outcomes and reduced rates of side effects. However, further investigation is needed [17].

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Vitiligo

69

Riad Kassem, Sharon Baum, and Aviv Barzilai

Abstract

Vitiligo is a common depigmenting autoimmune disease affecting 0.1–2% of the population worldwide. The characteristic white patches are due to the selective loss of melanocytes, which frequently affects the face and other visible areas of the body. Sometimes, the pigmented cells in the eyes and ears are also affected. This can be psychologically devastating and can impose a considerable burden on daily life, including stigmatization and social isolation, as observed in cases of other skin diseases, such as psoriasis and atopic dermatitis.

Vitiligo may be associated with other organ-specific autoimmune diseases, such as thyroid disease (Hashimoto's thyroiditis and Graves' disease), Addison's disease, pernicious anemia, insulin-dependent diabetes mellitus, and alopecia areata.

Until recently, only limited treatments were available for vitiligo. The therapeutic alternatives relied on drugs that nonspecifically target inflammatory and immune responses, such as topical and systemic steroids or topical calcineurin inhibitors, with or without ultraviolet light, to stimulate melanocyte regeneration, and several surgical techniques for resistant cases that have offered significant benefits to patients. Sometimes, the only alternative to treating generalized vitiligo with minimal pigmentation spots is to depigment the remaining pigmented epidermis.

In August 2022, for the first time, the Food and Drug Administration approved ruxolitinib, a JAK 1 and 2 inhibitor, as a topical medication indicated for vitiligo. This was a breakthrough in the field of dermatology and increased the hope of finding efficient medications for this persistent disease.

Keywords

Vitiligo · Melanocytes · Autoantibodies · JAK inhibitors · Autoimmune diseases

Epidemiology

Vitiligo is not inherited, but the predisposition to vitiligo is inherited; approximately 80% of the risk is attributable to genetic factors, and the rest is attributable to the environment. It is relatively frequent, with an estimated global prevalence of 0.1–2% in both adults and children [1]. All ethnic groups and skin types are equally affected, with no sex-related differences in prevalence reported. It can develop at all ages but most frequently in young people between the ages of 10 and 30 years.

Approximately half the people with vitiligo acquire the disease before the age of 20 years, resulting in a heavy burden of the disease and decreased quality of life, as seen in cases of other skin diseases, such as psoriasis and atopic dermatitis [2].

Vitiligo may be associated with other organ-specific autoimmune diseases, such as thyroid disease (Hashimoto's thyroiditis and Graves' disease), Addison's disease, pernicious anemia, insulin-dependent diabetes mellitus, and alopecia areata. One study reported that 34% of the patients tested positive for thyroid antibodies but without any clinical correlation [3].

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Pathogenesis

Vitiligo is a multifactorial disorder characterized by the loss of functional melanocytes. Multiple mechanisms have been proposed to explain the melanocyte destruction. These include genetic and autoimmune factors, oxidative stress, the generation of inflammatory mediators, and detachment of melanocytes. Both the innate and adaptive arms of the immune system are involved. However, none of these theories sufficiently explain the different vitiligo phenotypes. The overall contribution of each of these processes remains debated, although there is now a consensus regarding the autoimmune nature of vitiligo [4].

Genetic Aspect

Incidences of vitiligo affecting multiple close relatives are termed "multiplex" family clusters and represent only 9% of vitiligo cases; conversely, the vast majority of vitiligo cases (91%) do not have any known close relatives affected by vitiligo and are termed "simplex" [4].

Large-scale genome-wide association studies have revealed over 50 genetic loci that confer the risk of vitiligo. The corresponding genes have been identified in many of these vitiligo loci. These genes are involved in immune regulation, melanogenesis, and apoptosis and are associated with other pigmentary, autoimmune, and autoinflammatory disorders.

The other loci are components of the innate and adaptive immune systems and are shared with other autoimmune disorders, such as thyroid disease, type 1 diabetes, and rheumatoid arthritis, supporting their role in shared autoimmune predisposition. The variants with the greatest overall genome-wide impact on the disease risk were within the transcriptional enhancers located in the class I and class II regions of the major histocompatibility complex on chromosome 6 [5].

Oxidative Stress and Intrinsic Abnormalities in Melanocytes and Keratinocytes

Oxidative stress may be the initial event in melanocyte destruction. Melanocytes respond to stress by releasing reactive oxygen species (ROS). The production and accumulation of ROS trigger DNA damage, protein oxidation and fragmentation, and lipid peroxidation, which compromises cellular function [6].

Patients with vitiligo exhibit disrupted mitochondrial membrane function and mitochondria-dependent apoptosis in the melanocytes. Both keratinocytes and melanocytes release chemokine ligands that are important for the recruitment of T cells in response to oxidative stress.

Innate Immunity

Innate immune cells are likely activated early on in vitiligo by exogenously or endogenously induced stress signals released from the melanocytes and keratinocytes, with the subsequent activation of adaptive and memory immune responses.

Adaptive Immunity

Humoral and cell-mediated immune dysregulation is involved in the pathogenesis of vitiligo. Patients with vitiligo have antibodies against surface and cytoplasmic melanocyte antigens. However, these autoantibody titers do not correlate with vitiligo activity. Despite the autoantibodies being present systemically, vitiligo develops only in well-defined macules, suggesting that anti-melanocyte antibodies are not the main drivers of vitiligo pathogenesis [7].

Melanocytes are destroyed by cytotoxic CD8+ T cells that specifically target them. These cells are found in higher numbers in the blood of patients with vitiligo than in healthy controls, and these numbers correlate with vitiligo activity [8]. These CD8+ T cells produce several cytokines in vitiligo lesions, including interferon-γ (IFNγ) and tumor necrosis factor.

IFNγ is central to the pathogenesis of vitiligo and promotes recruitment of auto-reactive CD8+ T cells into the skin through a feedback loop. IFNγ induced the highest expression of CXC chemokine ligand 9 (CXCL9), CXCL10, and CXCL11 in the skin lesions of patients with vitiligo.

IFNγ signaling starts by its binding to its cell surface receptor (IFNgR), which forms a heterodimeric protein complex and recruits JAK1 and JAK2 kinases, leading to phosphorylation and nuclear translocation of STAT, which in turn transcriptionally activates downstream IFNγ-inducible genes [9].

JAK1 expression is much more intense and diffuses in the skin lesions of patients with vitiligo than in healthy tissues. High JAK1 expression was associated with short disease duration and a lower percentage of surviving melanocytes. All these findings provide the rationale for therapies that disrupt the IFNγ–CXCR3-CXCL9/10 axis and the downstream signaling proteins JAK1, JAK2, and STAT1 [10].

Diagnosis

Clinical Manifestations

Vitiligo appears as sharply circumscribed, cosmetically disturbing white spots. Its appearance is particularly noticeable when the unaffected skin is tanned. It is categorized based on the extent of involvement and distribution of depigmentation. Generalized vitiligo is the most common presentation of bilateral symmetric depigmentation of the face (especially the periorificial areas), neck, torso, extensor surfaces, and bony prominences of the hands, wrists, legs, axillae, or orifices. Mucus membrane involvement is frequently observed in patients with generalized vitiligo. Moreover, vitiligo often occurs around body orifices, such as the lips, genitals, gingiva, areolas, nipples, palms, and feet (Figs. 69.1 and 69.2). Segmental vitiligo occurs in a dermatomal, asymmetric distribution (Fig. 69.3). It is considered a special type of vitiligo due to its earlier onset, recalcitrant course, and decreased association with autoimmune disease [11].

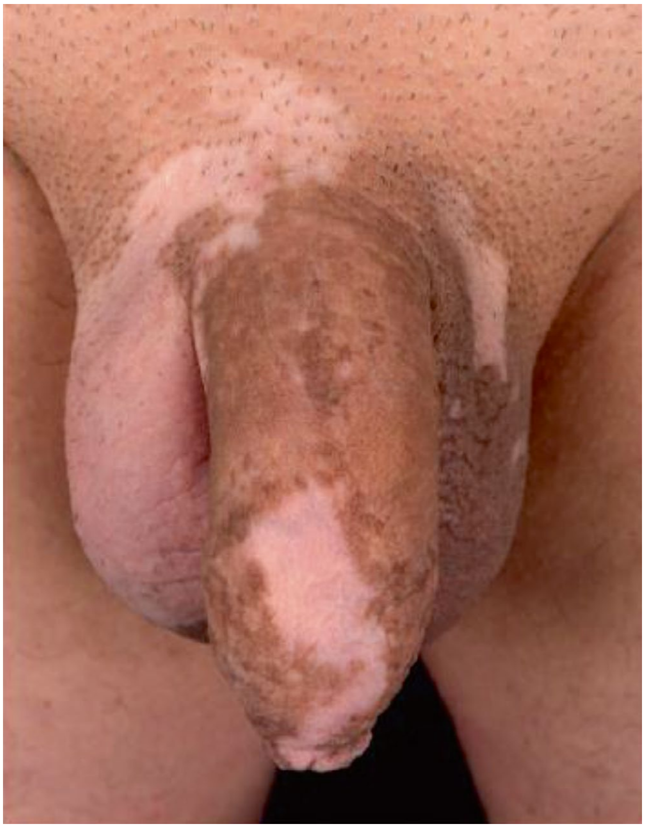

Fig. 69.1 Complete loss of pigment on the penis and scrotum. (*Courtesy, Lorenzo Cerroni, MD*)

Universal vitiligo refers to the loss of pigment over the entire body surface area. Most patients initially experience depigmentation upon exposure to sunlight. Depigmentation of body hair in the vitiliginous macules may be present. Although the color of the iris does not change in patients

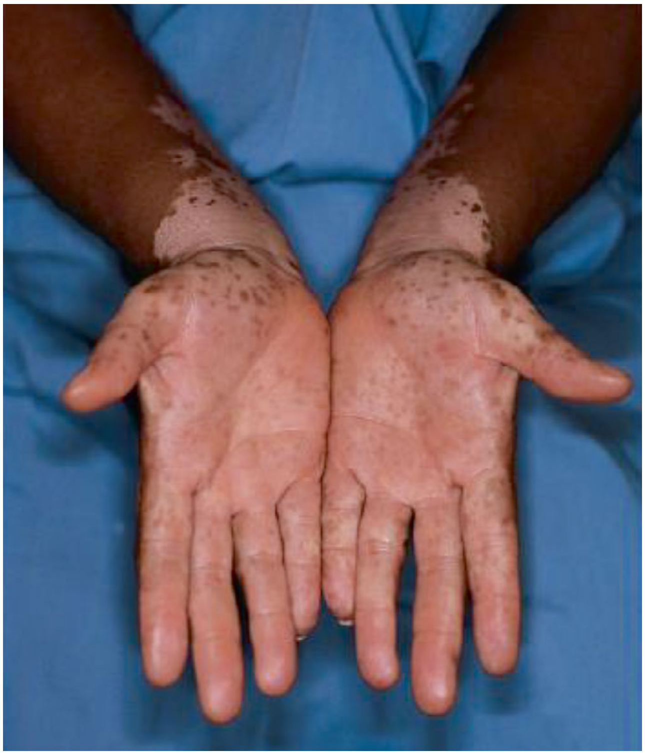

Fig. 69.2 Typical clinical picture of vitiligo involving volar wrists as well as palmar surfaces. (*Courtesy, Jean L Bolognia, MD*)

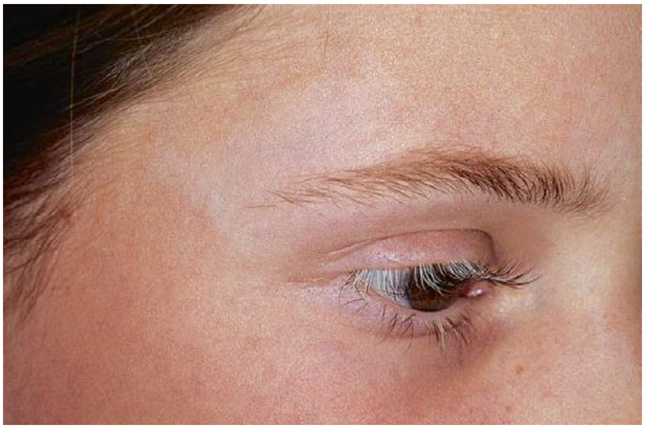

Fig. 69.3 Segmental vitiligo. Under normal light, the vitiligo can be subtle in lightly pigmented individuals. The evidence for the diagnosis is the poliosis of the eyelashes. (*Courtesy, Jean L Bolognia, MD*)

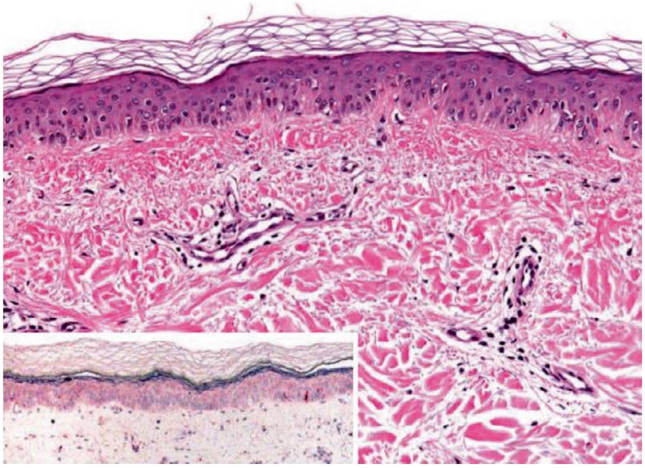

Fig. 69.4 Histological image of vitiligo. The complete absence of melanocytes in the basal layer of the affected epidermis is highlighted by Melan-A (MART-1) staining (insert), in contrast to the normal number of melanocytes visible in the adjacent unaffected skin on the lateral edge. (*Courtesy, Lorenzo Cerroni, MD*)

with extensive vitiligo, depigmented areas in the pigment epithelium and choroid occur in up to 40% of patients. Moreover, the incidence of uveitis in patients with vitiligo is higher than expected [12]. Melanocytes are present in the membranous labyrinth of the inner ear. As vitiligo affects all the active melanocytes, auditory problems may ensue. In a study of patients with vitiligo younger than 40 years of age, 16% had hypoacusis in the 2–8 kHz range, which is a minimal disturbance to those affected [13].

Pathology

Histologically, melanocytes are uniformly absent in vitiliginous skin, as supported by dopa- and silver nitrate-negative staining and by monoclonal and polyclonal antibodies directed against melanocytes. Rarely, perivascular or lichenoid lymphocytic infiltrates and melanophages, with only a slight decrease in the number of melanocytes, may be observed in the early lesions (Fig. 69.4).

A skin biopsy or other investigations are not necessary, except to exclude other skin diseases. The use of a Wood's lamp may help in the diagnosis of vitiligo and differentiate different types of depigmentation. Under Wood's light, vitiligo lesions emit a bright blue-white fluorescence and appear sharply demarcated.

Dermoscopic examination of vitiligo typically shows residual perifollicular pigmentation and telangiectasia, which are absent in other hypopigmentation disorders. This may be useful in monitoring disease activity and the stage of evolution.

Table 69.1 Main treatment strategies for vitiligo

Treatment	Localized disease	Diffuse disease
First line	TCI, TCS Topical JAK inhibitors	nbUVB phototherapy, Sys CS (weekend therapy)
Second line	Targeted phototherapy	Other immunosuppressants (MTX, CSA)
Third line	Surgical modalities	For exposed areas: surgical modalities, topical treatment, cosmetic camouflage

TCI topical calcineurin inhibitors, *TCS* topical corticosteroids, *nbUVB* narrow-band ultraviolet B, *Sys CS* systemic corticosteroids, *MTX* methotrexate, *CSA* cyclosporin A

Occasionally, the following specific tests are required to rule out the association with other autoimmune diseases: thyroid profile, blood sugar, complete blood count, vitamin B12, and iron levels.

Prognosis

The course of the disease is unpredictable but is often progressive with phases of stabilized depigmentation. An extending vitiligo with enlarging macules or the development of new lesions is classified as the active form of the disease.

Treatment

Disease management focuses on stopping the immune destruction of melanocytes, halting depigmentation, stabilizing depigmented lesions, stimulating repigmentation, and preventing relapse after repigmentation.

Several treatments are available, including phototherapy, topical and systemic immunosuppressants, and surgery (Table 69.1). Most therapeutic alternatives require at least 2–3 months to determine their efficacy, which is time-consuming and requires long-term follow-up.

Patients with vitiligo are suggested cosmetic camouflage by cosmeticians, especially when vitiligo affects the exposed areas.

Phototherapy The first modern use of light therapy in combination with purified topical and/or oral psoralens was performed by El Mofty in 1948. PUVA (psoralen with UVA) utilizes UVA light radiation (in the 320–400 nm range) along with either systemic or topical 8-methoxypsoralen. The UV light converts psoralen compounds into DNA-reactive oxidative chemical products that suppress the immune function and stimulate melanocyte proliferation and pigmentation [14].

These combined immunosuppressive and pigment-stimulating properties may explain the efficacy of PUVA as a treatment for vitiligo. Oral PUVA is used in patients with extensive vitiligo. Vitiligo on the trunk, proximal extremities, and face respond well to PUVA therapy, but the distal extremities and periorificial or dermatomal depigmentation do not. However, more recent clinical studies have revealed that radiation in the 311 nm range, known as narrow-band ultraviolet B (nbUVB) phototherapy, provides superior repigmentation of vitiligo lesions, with fewer adverse effects, such as gastrointestinal irritation and the increased risk of skin cancer noted in cases of PUVA therapy.

Similar to PUVA, nbUVB light suppresses cutaneous immunity while stimulating melanocyte proliferation and pigmentation. Thus, nbUVB has largely replaced PUVA as the first-line therapy for vitiligo. Conventional treatment strategies incorporate nbUVB phototherapy in combination with topical corticosteroids and/or topical calcineurin inhibitors. Currently, it is the treatment of choice for patients with moderate to severe vitiligo [15]. The major advantages of nbUVB treatment include ease of treatment, lack of need for post-treatment ocular protection, and absence of systemic side effects.

Targeted phototherapy with a 308 nm excimer laser may be more effective as it spares the uninvolved skin area, uses a lower cumulative dosage, and requires shorter treatment times, which may collectively reduce the incidence of long-term side effects of phototherapy [16].

Topical and Systemic Steroids One of the key points of treatment is the stabilization of the rapidly progressing disease. Patients can experience a rapid progression of vitiligo, with depigmented macules spreading over a few weeks or months. This requires urgent intervention with systemic oral mini-pulse steroids, a treatment that consists of corticosteroid administration twice weekly [17].

High-potency steroids, such as clobetasol, are used at localized, depigmented areas for 1–2 months, during which time the therapy is slowly tapered to a lower-strength preparation. However, repigmentation with steroids has yielded variable results. Moreover, systemic corticosteroid treatment is not warranted for the treatment of vitiligo due to its potentially severe side effects. The long-term follow-up of patients treated with topical steroids has been limited; therefore, it is difficult to ascertain their efficacy.

Topical Immunomodulators Since 2002, some topical immunomodulators have been used for the treatment of vitiligo either alone or in combination with other treatments including tacrolimus and pimecrolimus, with variable results. In a randomized, double-blind, right–left comparison study by Lepe et al., 20 children with active vitiligo were treated with 0.1% tacrolimus or 0.05% clobetasol twice daily for 2 months. The authors reported that tacrolimus was almost as effective as clobetasol [18].

Emerging Targeted Therapies In Vitiligo Major progress in the understanding of vitiligo pathogenesis and the key role of the immune system has led to the development of targeted therapies, some of which are currently being tested in clinical trials. In August 2022, the Food and Drug Administration approved ruxolitinib (Opzelura) for vitiligo. This was a breakthrough in the field of dermatology as this was the first treatment specifically indicated for vitiligo as most others were nonspecifically indicated [19].

Patients who used topical ruxolitinib 1.5% cream, a JAK-1/2 inhibitor, showed a significantly higher rate of repigmentation after 24 weeks than did patients in the placebo group. This promising result provides hope for the development of new medications in the future.

Surgical Treatment If topical therapy or phototherapy fails to induce repigmentation, surgical alternatives exist. These treatment regimens are often limited to segmental or localized vitiligo. Surgical modalities may be considered only in cases where the disease is inactive and non-progressive for at least a year. Moreover, areas, such as the dorsal fingers, ankles, forehead, and hairline, tend not to repigment well. Treatment alternatives include epidermal grafting, autologous minigrafting, transplantation of in vitro cultured epidermis, and non-cultured melanocytes [20].

Cosmetic Modalities

Visible depigmented macules and patches can be concealed using makeup or topical dyes. The cost, ease of application for focal vitiligo, and lack of side effects are the specific advantages of topical cover-ups. However, patients who are unaccustomed to wearing makeup, engage in vigorous physical activity, or have extensive disease may find topical cosmesis difficult.

Sometimes, the only alternative to treating generalized vitiligo with only a few spots of pigmentation is to depigment the remaining pigmented epidermis.

Conclusion

Despite the complex pathogenesis of vitiligo, targeted therapies with the potential to prevent, stop the progression of the disease, and even cure vitiligo are under development, with promising outcomes.

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Psoriatic Arthropathy

70

Elias Toubi

Abstract

Psoriatic arthritis (PsA) is a common inflammatory arthritis that characteristically occurs in individuals with psoriasis. Varied presentations of PsA may delay the timely diagnosis and treatment in some patients. The widely accepted CASPAR classification criteria are highly sensitive and specific and are frequently used as a diagnostic tool. New treatment modalities, particularly biological medicines, allow better control of diverse manifestations of PsA.

Keywords

Psoriatic arthritis · Psoriasis · Spondyloarthritidies · Dactylitis · Biological therapies

Introduction

Psoriatic arthritis (PsA) is a common inflammatory arthritis that characteristically occurs in individuals with psoriasis. PsA was classified as a distinct entity for the first time in 1964, but the antiquity of this disease may be measured by tens of centuries [1]. The many faces of PsA have historically complicated the timely diagnosis on the one hand, while its aggressive and destructive behavior has been recognized in up to 20% of affected persons on the other [2]. As such, PsA has attracted much attention in the last decades, resulting in significant progress in understanding, classifying, and treating the disease. This chapter will summarize the current experience in PsA in light of the recent developments in the field.

A Clinical Spectrum

Traditionally classified in the group of spondyloarthritidies (SpAs), PsA may manifest clinically the whole gamut of patterns that were first recognized by Moll and Wright (1973) [3]. Since then, many additional large series of patients with PsA have been published, and much new data has accumulated. We recognize today that PsA may not only be an oligoarticular or polyarticular disease or affect peripheral or axial joints or the spine, but it may also evolve from one pattern to another with time [4]. These patterns may also overlap, particularly in patients with longstanding disease. In most patients, PsA coexists with skin psoriasis, which may be extensive, limited, or even hidden, with a patient unaware of its existence.

On the contrary, in as many as 7–30% of patients, arthritis may precede the appearance of psoriatic skin lesions, called "PsA *sine* psoriasis" [2]. In these patients, where a primary prompt to the causation is absent, the correct diagnosis of PsA will depend solely on recognizing the specific features of the articular disease. Nevertheless, no single clinical, radiological, or laboratory sign pathognomonic for PsA has been reported, thus raising the expert physician diagnosis to the traditional gold standard in diagnosing PsA [5].

Of the five main patterns of PsA, both the ***oligoarticular*** and ***spinal*** variants may be challenging to distinguish from the other members of the SpA group [6]. By clinical presentation and radiological features, these two patterns of PsA are remarkably similar to reactive arthritis, while a broad spectrum of skin rashes and lesions occurring in the course of the latter may merely complicate the differential diagnosis. *Enthesopathy*, a characteristic feature of the whole SpA group, may be particularly prominent in PsA, frequently affecting plantar fascia or Achilles tendons. Bone marrow edema adjacent to entheseal insertion sites is characteristic in PsA and thought to be a manifestation of underlying osteitis. At the very earliest stage of PsA, this involvement of the entheses has also been demonstrated by magnetic resonance imaging (MRI) and has led to an enthesis-based biomechani-

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cal hypothesis of the disease's pathogenesis [7]. *Dactylitis*, an inflammation affecting both the joints and the tendons of the whole digit, may be seen in 16–48% of patients with PsA, being usually less common in other SpA. PsA is also featured by the relative asymmetry of sacroiliac/spinal involvement and more extensive paramarginal syndesmophytes and periosteal reaction compared to ankylosing spondylitis or SpA related to inflammatory bowel disease.

The evidence of SpA features (inflammatory enthesopathy, dactylitis, spinal involvement, periosteal proliferation) in any further discussed pattern of PsA is of primary importance and may serve as a clue to the proper diagnosis in many patients.

A distal pattern affecting the distal interphalangeal (DIP) joints must be mainly differentiated from osteoarthritis (OA), particularly inflammatory erosive OA. The joint involvement in these two disorders may be very similar clinically and radiologically. A clue to the correct diagnosis lies in the concomitant *psoriatic nail involvement* in most patients with PsA. Pitting is the most common psoriatic nail lesion, while onycholysis, nail-bed discoloration, subungual hyperkeratosis, transverse grooves, or longitudinal ridging may also be seen [8]. Notably, nail changes were reported to occur in about 90% of patients with PsA (all patterns), compared with 45% of psoriatic patients without arthritis. The MRI studies demonstrated that involvement of the distal phalanges in the inflammatory process accompanies both the DIP joints' involvement and psoriatic nail lesions in patients with PsA, a potential connective link between the two phenomena [9].

Laboratory parameters of inflammation (erythrocyte sedimentation rate and C-reactive protein) are frequently normal or minimally elevated in PsA, not contributing much to the differential diagnosis in this setting. However, the fine interpretation of X-rays may help to differentiate between PsA and OA in some patients. The lack of apposition of adjacent bony margins would be characteristic of PsA, while undulating osseous surfaces are usually closely applied in OA. If they exist, the pencil-in-cup appearance of the joints, irregular periosteal bone proliferation, or resorption of the distal tuft may be diagnostic for PsA.

A polyarticular pattern must be distinguished from rheumatoid arthritis (RA). In this setting, PsA may be recognized by its tendency to asymmetry and involvement of the joints in the "ray" pattern rather than in the "row" pattern typical for RA. The presence of erythema over the inflamed joint is unusual in RA but may be seen frequently in PsA, probably reflecting the characteristic of psoriatic disease: exaggerated angiogenesis. Concomitant involvement of DIPs, spine, or psoriatic nail lesions in PsA patients should not go unnoticed. Positive serology, both RF and anti-cyclic citrullinated peptide [anti-CCP] antibodies, typically associated with RA, may sometimes be deceiving, occurring in PsA (mainly polyarticular) in up to 10–15%. Intriguingly, an association of a positive test for anti-CCP antibodies and HLA-DRB1-shared epitope was reported in patients with PsA [10]. Radiologically, both PsA and RA are characterized by osseous erosions; however, irregular excrescences of bony proliferation and the lack of juxta-articular osteoporosis would strongly favor the diagnosis of PsA.

Arthritis mutilans is the most destructive form of PsA, which may lead to extensive and irreversible joint damage with the appearance of the "telescoping" phenomenon and shortening of the digits in a short time. The abovementioned clinical and radiological features of PsA may contribute to the diagnosis, necessitating an aggressive therapeutic approach.

Classification Criteria

At least six different criteria sets have been proposed since the first diagnostic criteria of Moll and Wright that included three main points: the existence of inflammatory arthritis, the presence of psoriasis, and seronegativity [3, 11]. The many patterns of PsA necessitated, however, more specific classification criteria to distinguish PsA from other members of the SpA group, OA, RA, or gout, which may be frequent in association with psoriasis. A case is even more complicated owing to the high prevalence of psoriasis and the aforementioned rheumatic diseases, leading to a statistically sensible noncasual association of skin psoriasis and arthropathies.

In 2006, an international group of experts in PsA, the **cLAS**sification of **P**soriatic **AR**thritis (CASPAR) study group, worked out new simple and highly specific classification criteria [5]. These criteria permit the classification of inflammatory articular disease as PsA when at least three of the following (current psoriasis gains 2 points, each other criterion gains 1 point) are met:

- Current psoriasis (2 points) or personal or family history of psoriasis
- Typical psoriatic nail dystrophy
- Dactylitis
- Negative test for rheumatoid factor
- Juxtaarticular new bone formation (excluding osteophytes) on plain radiographs of the hand or foot

The CASPAR criteria, developed based on data analysis of 588 patients with PsA and 534 patients with other arthropathies, have a specificity of almost 99% and a sensitivity of 91.4%. In addition to their very high specificity, the CASPAR criteria are also progressive by permitting the diagnosis of PsA in the absence of psoriasis (PsA sine psoriasis) and in RF-positive patients. Excellent performance of the CASPAR criteria was also shown in early PsA [12].

A detailed comparison of the historical and current diagnostic and classification criteria for PsA may be found in [5, 11].

PsA Mechanisms

The understanding of cellular interactions and molecular pathways of inflammation in PsA has significantly improved over the last decades [13, 14]. In general, synovial histopathology of PsA, whether oligo- or polyarticular, appears closer to that of other SpA than RA. Notably, *increased synovial vascularity*, triggered by vascular growth factors, and massive *neutrophil infiltration* are characteristic of PsA [15]. Of interest, both increased angiogenesis and abundance of neutrophils are also seen in psoriatic skin lesions.

Intracellular citrullinated peptides, frequently recognized in RA synovium, are not seen in PsA [15]. Besides neutrophils, the synovial infiltrate in PsA is formed mainly by T lymphocytes, with cells of B-lineage, macrophages, and dendritic cells present. Both CD4 and CD8 *T cells*, with the latter predominating in the joint effusions in PsA, may show oligoclonal expansions, suggesting an antigen-driven response [16]. Th17 lymphocytes and type 3 innate lymphoid cells, both producing IL-17 and IL-22, are also increased in the joint fluid in PsA [17]. *B cells* present in the PsA synovium participate in building lymphoid aggregates there, which may point to antigen-driven B-cell development as part of PsA pathogenesis [18]. However, the precise organization and function of B cells in PsA are unclear. *Macrophages*, which usually serve as a leading source of TNF-α, may differ in the inflamed synovium of PsA from that in RA by their numbers and subtypes, with more CD163+ macrophages found in PsA [15]. *Dendritic cells* (DCs) have recently attracted much attention as potential key players in psoriasis and PsA. Plasmacytoid CD123+ DCs serve there as major interferon-α producers, while myeloid CD11c+ DCs produce a variety of cytokines, including IL-23, leading to the increased production of Th17 lymphocytes and orchestrating the whole gamut of the immune response [14]. Accordingly, cytokine pathways based on the *TNF-α* and *interleukin-23/interleukin-17* cytokine networks have been recently shown to play central roles in the pathogenesis of PsA (reviewed in [14]).

Disturbed bone remodeling, expressed by extensive bone erosions and exaggerated bone formation in the same patients, is another characteristic and poorly understood feature of PsA. The receptor activator of nuclear factor-kappa B ligand (RANKL), TNFα, and IL-7 have been recently suggested as critical molecules activating osteoclasts and subsequent bone resorption in PsA [19]. Interleukins 17 and 22, as well as molecules of the *Wnt* signaling pathway and bone morphogenic proteins, have been suggested as central players in the mechanisms characteristic for PsA increased bone formation [13].

PsA Treatment

A better understanding of disease mechanisms allowed for the introduction of new, highly specific, and effective therapies for PsA in the past decades. Some therapies were translated to the field of PsA from the experience with RA and AS patients, while others were first used in patients with psoriasis. This new generation of biological medicines differs from traditionally used in PsA methotrexate, sulfasalazine, cyclosporine, and other disease-modifying anti-rheumatic drugs (DMARDs) by their targeted action on a specific structure, leading to the neutralization of this structure (i.e., anti-TNF treatments) or interruption of immunological signal transduction and modulation of T-lymphocyte function [20].

The enhanced efficacy of biologicals in PsA has been repeatedly appreciated in clinical trials and confirmed by evidence-based studies (reviewed in [13]). The broad spectrum of currently available therapies for PsA allows the implementation of coordinated therapeutic strategies directed at both psoriatic skin lesions and various domains of PsA [21].

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Autoinmune Alopecia/Alopecia Areata

71

Andrea Combalia

Abstract

Autoimmune alopecia or alopecia areata (AA) is an autoimmune nonscarring alopecia characterized by sudden and patchy hair loss that can affect any hair-bearing area. The diagnosis of AA is clinical but can be supported by trichoscopy, and skin biopsy and histological examination are only performed in selected cases. Mild episodes with a duration of less than 12 months may resolve spontaneously; however, extensive alopecia areata is unlikely to remit without treatment. Classical management is guided by the degree of scalp and body involvement, with topical and intralesional steroid injections as primarily first-line for mild cases, and oral corticosteroids and broad immunosuppressants. However, the recent US FDA-approved Janus kinase (JAK) inhibitors for AA, baricitinib (2022) and ritlecitinib (2023), are a promising drug class for treating severe alopecia areata cases. Moreover, the landscape of treating still has the potential to be transformed, as several novel targeted drugs are currently undergoing clinical trials.

Keywords

Alopecia areata · Janus kinase inhibitors (JAKi) · Skin biopsy · SALT score · Baricitinib · Ritlecitinib · JAK-STAT · Hair loss

Introduction

Alopecia areata (AA) is an autoimmune disorder characterized by sudden and patchy nonscarring hair loss that can affect any hair-bearing site. The lifetime risk of developing AA in the general population is estimated at 2%, with a prevalence of approximately 1 in 1000. Both children and adults may develop alopecia areata, and the disorder occurs at similar rates in males and females.

Evidence suggests that the cause of the condition is autoimmune, with a significant genetic contribution, which is further influenced by unknown environmental factors. Reported triggers include emotional or physical stress, vaccinations, viral infections, and medications [1].

The disease is mediated by T lymphocytes against aberrant HLA-RR expressed by keratinocytes of the hair follicles. Cytokines that are implicated in pathogenesis, including interferon-γ and interleukin-15, depend on Janus kinases (JAKs) for intracellular signaling. As a result, inflammatory cells target the hair follicle matrix epithelium undergoing early cortical differentiation (anagen hair follicles), prematurely pushing them into the catagen or telogen phase [2, 3].

Clinical Presentation

Alopecia areata often presents as isolated, smooth, nonscarring round patches of hair loss, typically on the scalp, but it can occur anywhere with hair growth (Fig. 71.1). Some patients may progress to total hair loss on the scalp (a condition known as alopecia areata totalis) or experience a complete hair loss over the entire body (a condition known as alopecia universalis).

Moreover, approximately 10–15% of patients experience nail involvement, characterized by fine nail pitting, trachyonychia, onychorrhexis, red spotting on the lunulae, onycholysis, and onychomadesis.

Individuals with alopecia areata also have an elevated risk of suffering from other autoimmune diseases such as vitiligo, celiac disease, lupus, thyroid disorders, and atopic dermatitis.

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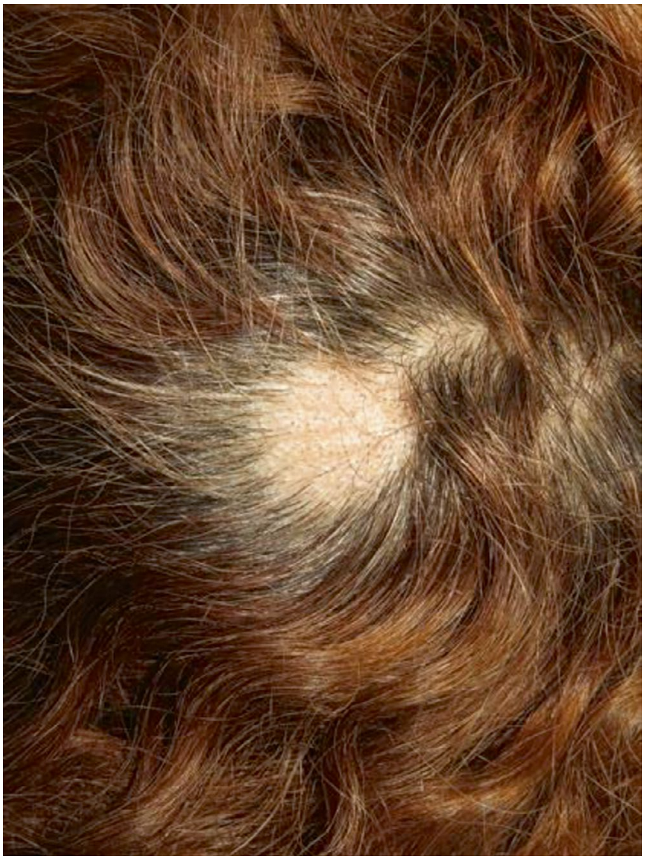

Fig. 71.1 Clinical presentation of patchy alopecia areata

SALT Score

The Severity of Alopecia Tool (SALT) is a standardized method for quantifying scalp hair loss in alopecia areata used in clinical practice to assess the severity of the disease. The SALT score measures hair loss on a scale of 0 (no scalp hair loss) to 100 (complete scalp hair loss). For example, SALT 20 can be defined as 20% scalp hair loss and/or 80% scalp hair coverage. A SALT score of 50 or greater is generally considered a severe disease [4].

The SALT score is calculated by multiplying the percentage of scalp hair loss in each of the 4 quadrants of the scalp by the quadrant surface area and adding the 4 values together for a composite score. See Fig. 71.2.

Quality of Life Involvement

Alopecia areata can negatively affect the quality of life (QoL) and is associated with increased prevalence of anxiety and depression. Patients' perception of severity and the presence of eyelash and eyebrow hair loss are also impactful and should be considered in defining the severity of the disease. Therefore, although alopecia areata severity is often defined by the degree of scalp hair loss, its impact on QoL can also be a defining measure of severity [5, 6].

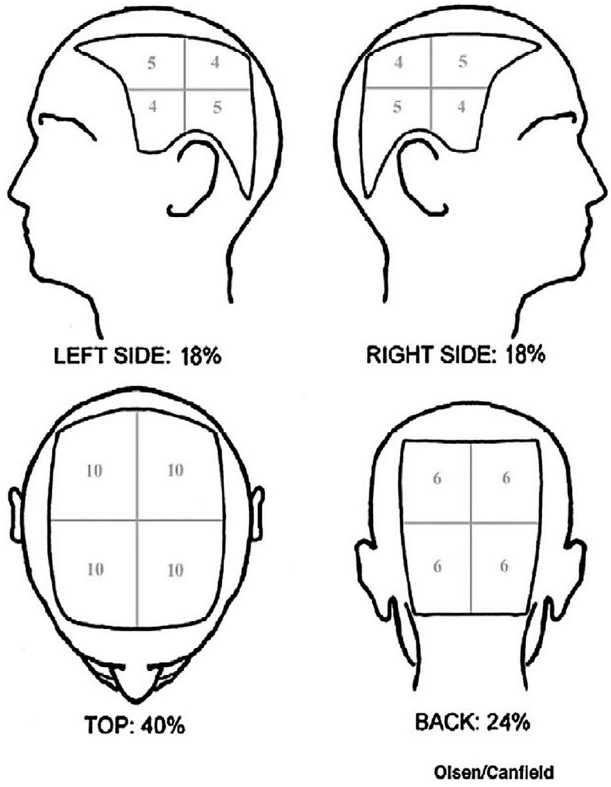

Fig. 71.2 Measurement of SALT score. Olsen/Canfield tool for determination of % scalp hair loss [4]

Diagnosis

The diagnosis of AA is clinical but can be supported by trichoscopy, a simple, rapid technique that reduces the need for invasive procedures, and can also help with monitoring treatment response. Skin biopsy and histological examination confirm the diagnosis; however, this is only performed in selected cases.

Trichoscopy

Trichoscopy with polarized light contact dermoscopy is a fast, non-invasive, and easy-to-perform technique that may help to identify subtle details and establish the correct diagnosis.

The most characteristic trichoscopic findings in AA are yellow dots, black dots, broken hairs, short vellus hairs, and tapering hairs (Fig. 71.3). However, there is no single pathognomonic trichoscopic sign in AA, but rather a constellation of characteristic findings. Yellow dots and short vellus hairs

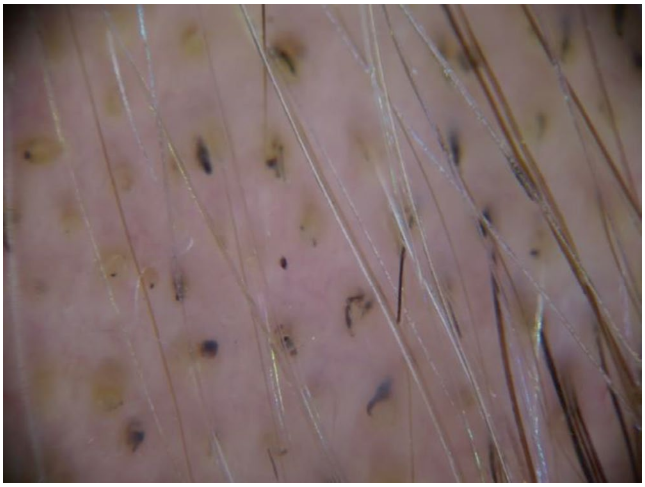

Fig. 71.3 Tricoscopic examination of active alopecia areata. Yellow dots, black dots, broken hairs, and tapering hairs can be observed

are considered the most sensitive clues for AA, while black dots and tapering hairs are the most specific ones. Furthermore, trichoscopy is a useful tool that allows monitoring of response during the treatment of AA. Treatment responded cases will show an increase in short vellus hairs but loss of tapering hairs, broken hairs, and black dots, while yellow dots are the least responsive to the treatment [7–9].

Histological Examination

From the histopathological point of view, alopecia areata is characterized by the presence of an inflammatory infiltrate of small lymphocytes that surround the bulb of the follicles in anagen, thereby inducing early conversion to catagen and telogen. The lymphocytic infiltrate comprises CD8+ T cells within the follicular epithelium and CD4+ T cells around the hair follicles. Histiocytes, plasma cells, mast cells, and eosinophils can also be observed. However, the characteristic inflammatory infiltrate that is normally observed in alopecia areata may be absent at times, particularly in cases of long-standing disease [10, 11].

Treatment

Mild episodes (SALT < 30) with a duration of less than 12 months may resolve spontaneously; however, extensive alopecia areata is unlikely to remit without treatment.

Classical management is guided by the degree of scalp and body involvement, with topical and intralesional steroid injections as primarily first-line for mild cases and oral corticosteroids and broad immunosuppressants (mainly methotrexate and ciclosporin) as the mainstay for more severe cases. All these classical treatments used for AA are used off-label with variable efficacy, limited therapeutic options, and no cure. Although medication can sometimes induce sustained remission, disease control cannot be guaranteed, and even those who regrow all hair on treatment can experience relapse. Moreover, in severe cases, the long-term use of high doses of corticosteroids and immunosuppressants can result in several severe adverse effects, some of which are irreversible [12].

The recent US FDA-approved Janus kinase (JAK) inhibitors for AA, baricitinib (2022) and ritlecitinib (2023), are a promising drug class for treating severe alopecia areata cases. They work by inhibiting enzymes involved in the transmission of information from receptors located in the cell membrane to the cell interior, specifically to the cell nucleus, thus disrupting the JAK-STAT pathway [13].

Baricitinib is the first FDA-approved treatment for AA after two multicenter, placebo-controlled phase III trials (BRAVE-AA1 and BRAVE-AA2) achieved clinically meaningful outcomes for scalp, eyebrow, and eyelash hair regrowth in patients with severe alopecia areata (AA). Baricitinib, an oral, selective, reversible inhibitor of Janus kinases 1 and 2, may interrupt cytokine signaling implicated in the pathogenesis of alopecia areata. It can modulate downstream inflammatory responses via JAK1/JAK2 inhibition and has exhibited a dose-dependent inhibition of IL-6-induced STAT3 phosphorylation. In the two large AA trials, AEs were considered mild or moderate; those reported more often with baricitinib than placebo included acne, elevations of low- and high-density lipoprotein cholesterol, and elevation of creatinine kinase. Baricitinib is a relatively tolerable and safe therapeutic alternative for severe AA, although additional study is needed to assess its long-term efficacy and safety in AA patients [14–17].

Ritlecitinib, the second FDA-approved treatment for alopecia areata based on the results of the ALLEGRO phase 2b/3 trial, is an oral, selective dual JAK3/TEC family kinase inhibitor that also interrupts cytokine signaling implicated in the pathogenesis of alopecia areata. Ritlecitinib is well tolerated and offers a therapeutic alternative for severe AA in patients who are candidates for systemic therapy [18].

As seen, the landscape on treating alopecia areata has changed since 2022 and still has the potential to be transformed, as several novel targeted drugs are currently undergoing clinical trials.

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72

Hidradenitis Suppurativa

Priscila Giavedoni and Irene Fuertes de Vega

Abstract

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease that can significantly affect patient quality of life. It presents with cutaneous nodules, abscesses, and tracts that are painful and recurrent. The lesions produce foul-smelling discharge and mainly affect intertriginous areas. HS has an estimated overall prevalence in the range of 0.1–2%. A diagnostic delay of up to 7–10 years is typical. The diagnosis of HS is usually made based on clinical findings. However, with cutaneous ultrasound, we can see incipient signs in these images that precede clinical onset, and we can detect deep lesions that would otherwise be clinically unsuspected. The Hurley staging system is still widely used in grading severity and is complemented and enhanced by the ultrasound Hurley scale. HS is associated with metabolic syndrome, other cardiovascular disease risk factors, depression, and substance use disorders. It has also been associated with other autoinflammatory diseases, such as inflammatory bowel disease, psoriasis, and spondyloarthropathy.

HS is a complex disease that requires an interdisciplinary approach to ensure the best outcomes in severe cases.

Keywords

Hidradenitis suppurativa · Acne inversa · Fistulas · Dermatology · Ultrasound

Description of the Disease

Hidradenitis suppurativa (HS) is a complex chronic inflammatory disease that damages the follicular portion of the folliculopilosebaceous unit (PFU). It has a prevalence ranging from 0.1% to 2% and is more common in women. The most frequent age of onset is in adolescence, although cases with onset over 40 years of age are not uncommon. The most affected areas are the folds: mainly the armpits and groin. However, this disease can involve any site containing PFU, such as the submammary area, intergluteal fold, perineum, buttocks, breasts, back, scalp, and genitalia [1].

There are several factors closely associated with the debut and progression of HS. Notable among these factors are smoking and overweight, which disproportionately affect patients with HS and whose control may be fundamental in the management of the disease [2].

The clinical expression is variable, ranging from mild cases with isolated inflamed nodules known as "swallows" to severe cases presenting persistent lesions such as tracts or scarring. All these lesions have a similar evolution, i.e., outbreaks with oozing of foul-smelling contents in the acute phase and scars that may form large fibrotic bands in the chronic phase (Fig. 72.1). The severe disease often profoundly impacts patient quality of life, as the foul odor, suppuration, and pain significantly limit all aspects of their life [3]. Diagnosis is fundamentally clinical. Doppler ultrasound allows for early diagnosis and staging, and magnetic resonance imaging helps to accurately delimit the deeper lesions [4]. An early and accurate diagnosis facilitates initiating a treatment plan aimed at minimizing the risk of progression to severe and disabling disease.

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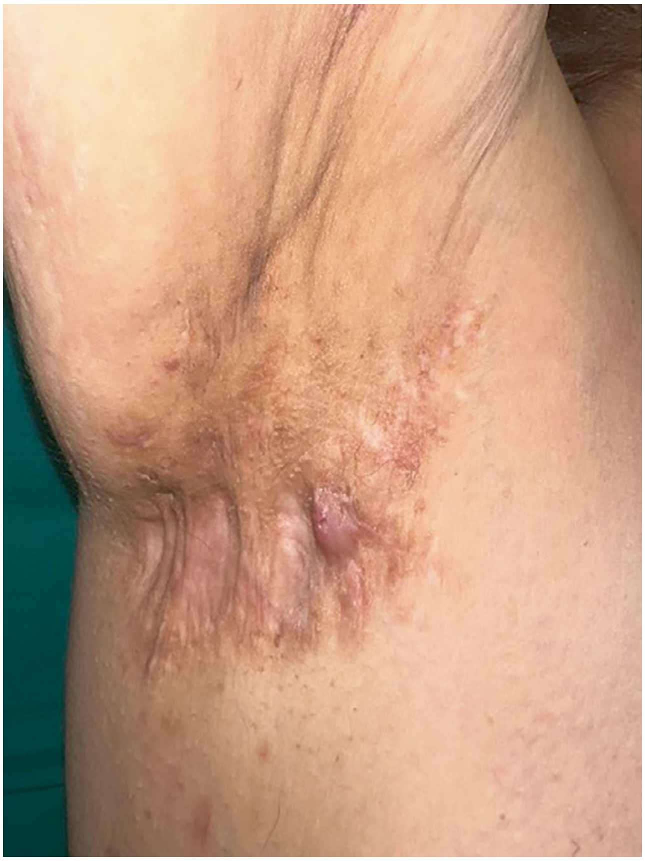

Fig. 72.1 Hidradenitis suppurativa. Thick fibrotic bands in the axilla that limit mobility

Microbiology, Serological Markers, and Genetic Tests

The skin of asymptomatic HS patients in areas where outbreaks usually occur harbors fewer bacteria than healthy controls. These data reveal the importance of the microbiota and the possible interactions it may have with inflammatory cytokines [5]. Cultures of suppurative lesions often contain gram-positive cocci and gram-negative organisms. Biofilms of bacterial aggregates are associated with inflammation of lesions, especially in fistulas, and could be a therapeutic target in the future [6]. However, culture lesions are not recommended unless secondary infection is suspected. Biomarkers are valuable in determining the severity of the disease and the response to treatment. The most commonly used of these are white blood cell count, erythrocyte sedimentation rate, and C-reactive protein, which are elevated in patients with severe disease and those who do not respond to treatment. When increased, other biomarkers that suggest active disease are TNF, IL-6, IL-17, soluble interleukin-2 receptor, and lipocalin-2. Patients with mild disease and those who respond to treatment have a lower expression of leukotriene A4-hydrolase, follicle-stimulating hormones, human chorionic gonadotropin, and luteinizing hormones. Genetic susceptibility plays a significant role as up to 40% of patients with HS have an affected first-degree relative [7]. Mutations in the γ-secretase/Notch pathway and dysregulation in the innate and adaptive immune pathways, such as those mediated by type 1 and type 17 T-helper cells, are the most commonly described, and polymorphisms in the TNF gene may also play a role in susceptibility to HS [8, 9]. However, it is rare to find known mutations in patients, despite the presence of familial aggregation.

Clinical Manifestations and Ultrasound Signs

Oozing, pain, and foul odor are the main symptoms of HS lesions. The disease predominantly occurs in intertriginous areas, with the axillae and groin being the most commonly affected. In addition, the inner thighs, the perianal and perineal areas, the mammary and inframammary regions, the buttocks, the pubic region, the scrotum, the vulva, the trunk, and occasionally the scalp and retro-auricular areas are also affected. It is a pathology with a slight predominance in women. Moreover, the distribution is different in men and women, with the axillary and upper trunk disease predominating in the latter and the inguinal, perineal, and perianal disease predominating in the former [10].

The most frequent age of onset is adolescence, although cases with onset over 40 are also observed. Sporadically, cases of early-onset HS are observed, which is usually associated with an increased risk of generalized disease [7].

Initial changes are subclinical and can be observed with high-resolution Doppler ultrasound. Table 72.1 describes the

Table 72.1 Percentages of cases with subclinical ultrasound signs of HS according to the sonographic staging

Early ultrasound signs of HS	SOS-HS 1	SOS-HS 2	SOS-HS 3
Curved hair follicles	99	100	100
Bilaminar hair tracts	100	98	100
Trilaminar hair tracts	10	20	7
Ground hypoechoic keratin	99	100	100
Sword sign[a]	12	9	37
Bridge sign[a]	57	67	85
Ballooning of the hair follicles	90	98	100
Communications of key lesions with the hair follicles	96	100	100
Donor sign	43	96	100
Heterogeneous involvement of hair follicles	100	100	100
Retained fragments of hair tracts	78	93	100
Retained cylindrical fragments of keratin[a]	46	51	78
Multiple fragments of keratin within the hair follicles	100	100	100
Double row or increased number of apocrine glands	18	0	0

SOS-HS sonographic staging of hidradenitis suppurativa [11]

[a] Significantly linked to the severity

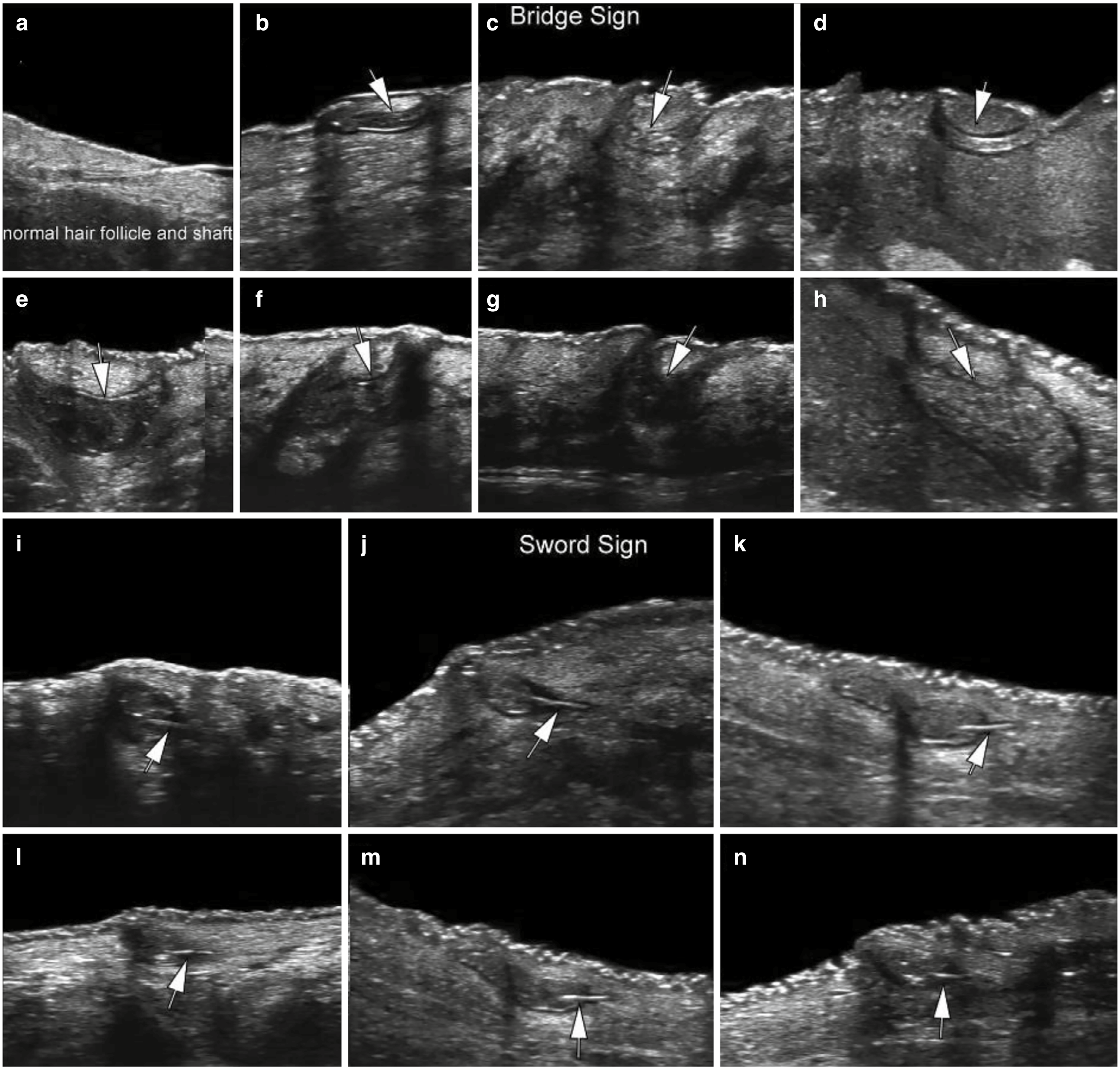

Fig. 72.2 Hidradenitis suppurativa: early ultrasound signs significantly linked to severity. On top, there are hypoechoic bands connecting adjacent and dilated hair follicles (bridge sign; (**a**–**h**), arrows pointing down) in comparison with a normal hair follicle (**a**). At the bottom, there are fragments of hair shafts extruding through the hair follicles in different cases (sword sign; (**i**–**m**), arrows pointing up) [11]

sonographic signs of HS, which range from abnormal curvature of hair follicles to extensive tunneling. Some of the sonographic signs are related to severity: the band of connection between the base of adjacent hair follicles (bridge sign), a fragment of the hair shaft protruding through a dilated hair follicle (sword sign), and cylindrical fragments of keratin retained in the dermis [11] (Fig. 72.2).

When the disease is clinically visible, the sonographic lesions can be pseudocysts, which are located in the dermis; fluid collections, which usually affect the dermis and hypodermis; and finally, fistulas, which can involve both the skin and the muscle, and even produce ulceration. When assessed by clinical examination alone, it is often impossible to know whether the observation corresponds to a superficial lesion or a deeper fistula, so ultrasound is essential for staging the disease. In addition, initial lesions that present as nodules are frequently diagnosed as superficial abscesses, and there is often a diagnostic delay of years until HS is correctly diagnosed [12].

The number and frequency of lesion flares vary widely among patients. In chronic and inactive phases, clusters of open comedones and scars are observed, ranging from small

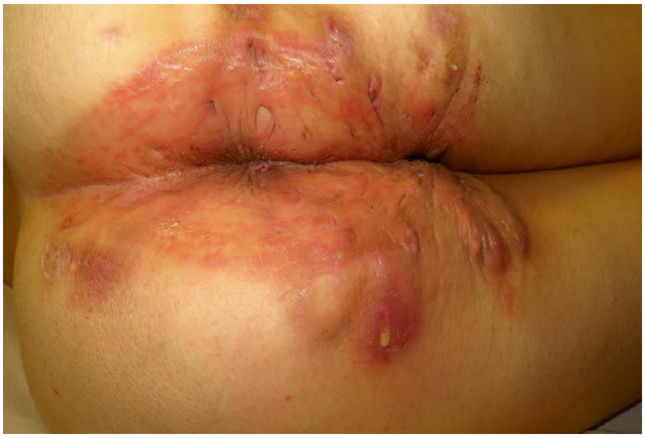

Fig. 72.3 Diffuse involvement of the intergluteal fold, with multiple fistulas and interconnected skin abscesses throughout the area

nodules and acne-like scars to large fibrotic bands that limit mobility and may even cause lymphedema in different regions, e.g., the vulva, penis/scrotum, and limbs, due to lymphatic obstruction of these areas [12]. In addition, pyogenic granulomas may develop at cutaneous fistula openings.

The Hurley scale classifies patients with HS into three disease severity groups:

Stage I—Abscess formation (single or multiple) without cutaneous fistulas or scarring/scarring
Stage II—Recurrent abscesses with cutaneous fistulas and scarring; single or multiple widely separated lesions
Stage III—Diffuse or near diffuse involvement or multiple interconnected skin fistulas and abscesses over the entire area (Fig. 72.3)

Fortunately, most patients are in stage I [13]; however, it is essential to detect disease progression in order to act before extensive fistulous tracts form, which are refractory to most medical treatments.

The Hurley scale is static and not very useful for assessing the evolution of patients and their response to treatment. For this reason, different classifications have been created to assess patients with HS. The Sartorius Hidradenitis Suppurativa Score, the Hidradenitis Suppurativa Physician Global Assessment (HS-PGA), and the Hidradenitis Suppurativa Severity Index (IHS4) are, despite their limitations, some of the most widely used.

Complications

When patients have a severe disease, depression is one of the most frequent and challenging complications as the associated social isolation, together with the pain, may lead to substance abuse and suicidal ideation [14].

As mentioned in the section on clinical manifestations, extensive and thick scars can act to limit movement and can also obstruct the lymphatic system, generating lymphedema in the affected areas [15].

In addition, like other chronic inflammatory diseases, HS can be complicated by anemia, hypergammaglobulinemia, hypoproteinemia, and even secondary amyloidosis. In patients with long-standing disease with persistent ulcerated lesions, squamous cell carcinoma should always be ruled out as a complication, which, fortunately, is rare [16].

Finally, since the cutaneous barrier is altered, infections are another potential complication, with sacral osteomyelitis being among the most severe.

Associated Diseases and Differential Diagnoses

One of the most frequent conditions in patients with HS is acne vulgaris, which may be present at the time of diagnosis and can be particularly severe and difficult to treat. It often manifests with deep and extensive scarring from previous outbreaks.

Moreover, HS can be a component of the follicular occlusion tetrad and manifest itself in addition to acne, with dissecting cellulitis of the scalp and pilonidal sinus.

As with other chronic autoinflammatory diseases such as psoriasis, patients with HS have a higher incidence of metabolic syndrome; in addition, many patients suffer from depression due to the symptoms of the disease and have higher rates of smoking. Different studies also suggest an association between HS and inflammatory bowel diseases, especially Crohn's disease and ulcerative colitis [17]. Some genes have even been associated with both conditions, such as SULT1B1 and SULT1E1.

HS can also occur within complex inflammatory syndromes, such as PAPASH syndrome (pyogenic arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa), with the term PASH syndrome being used to refer to patients with pyoderma gangrenosum, acne, and hidradenitis. Finally, HS has been associated with genetic alterations such as Down syndrome, Dowling–Degos disease, KID syndrome, and congenital paronychia [18].

Differential diagnoses include other diseases that cause inflamed nodules, recurrent abscesses, or fistulas.

Infectious folliculitis and boils can produce inflammatory lesions that are clinically very similar to HS. The diagnostic key is that HS usually has a chronic and recurrent course, whereas folliculitis and boils are usually isolated and resolve rapidly with appropriate antibiotic treatment. Other infectious diseases that can mimic HS and that can be confirmed via cultures, blood tests, and specific stains are lymphogranuloma venereum, syphilis in its nodule or ulcerated presentation, verrucous tuberculosis, actinomycosis, and granuloma inguinale caused by *Klebsiella granulomatis*.

Certain comorbidities of HS may be mistaken for manifestations of the disease. These include inflammatory acne, intergluteal pilonidal disease, and dissecting cellulitis of the scalp. Acne causes nodules and scars, mainly affecting the face, neckline, and back, but the lesions are usually more superficial than those of HS. Intergluteal pilonidal disease manifests as a skin cavity or fistula that can become inflamed and produce copious discharge. Dissecting cellulitis of the scalp also manifests with fistulas and scarring. These three entities appear to be part of the spectrum of HS and, as previously mentioned, constitute the follicular occlusion tetrad. Therefore, they can be considered differential diagnoses or clinical manifestations within the same entity.

The perianal and vulvar lesions associated with Crohn's disease include abscesses, rectoperineal and rectovaginal fistulas, cutaneous fistulas, and scars. Although it can be a differential diagnosis, the possibility of both diseases presenting simultaneously in some patients should be considered.

Current Diagnostic Criteria: Strengths and Limitations

As mentioned above, the diagnosis of HS is eminently clinical. However, diagnostic criteria for HS are considered to be the presence of the following:

Recurrent painful/suppurative lesions (2 or more in 6 months)
- Type of lesions: nodules, tracts, abscesses, and scarring
- Location: axilla, genital, inguinal, perineum, buttocks, and inframammary area in females

Various studies show that the degree of severity is modified in the majority of patients affected by stage I (mild) or II (moderate) HS according to the clinical Hurley classification when a cutaneous ultrasound is performed. Thus, clinical examination alone often underestimates HS and can, thus, lead to undertreatment. In many cases, tracts are not clinically visible and are only diagnosed with ultrasound.

In this disease, skin biopsies, blood tests, and/or genetic studies are not necessary to make the diagnosis. These techniques are used to assess the severity of the disease and detect complications, associated diseases, and predisposing genetic factors.

Once the clinical-echographic diagnosis has been made, counting and classifying the inflammatory lesions are suggested. It is essential to perform assessments that grade the pain and the effects on the quality of life of these patients in order to evaluate the response to the treatments performed.

A limitation that can delay diagnosis is the range of specialists presented with the disease, i.e., it is common for dermatologists, surgeons, family physicians, internists, and emergency physicians to see affected patient and these physicians are often unfamiliar with the diagnostic criteria of the disease.

Therapy and Prevention

Depending on the severity of the disease, the comorbidities, the cost of treatment, and, therefore, the availability of drugs in each work center, short-term topical antibiotics, oral antibiotics, surgical drains and resections, and biological treatments can be used.

For many patients, controlling factors associated with HS such as smoking and overweight are key to improving the disease [19].

Considering that HS is a progressive disease that evolves into persistent and fibrotic lesions, it is important to take into account the timing when dealing with HS. The concept of "therapeutic window," as the period of time in which we can act by preventing the formation of persistent lesions, is of great importance.

Topical clindamycin is a good option as a maintenance therapy for many patients. Oral metformin may be also an option especially applicable in women who also have an associated polycystic ovary syndrome. Similarly, spironolactone, finasteride, and certain oral contraceptives can also improve the symptoms of HS and are also indicated in cases where signs of hyperandrogenism are observed.

In patients with moderate symptoms, one effective option to control outbreaks is the use of oral antibiotics. The oral doxycycline regimen is a good option, which is equally effective and better tolerated than classical antibiotic therapy with clindamycin plus rifampicin. However, one tries to use oral antibiotics sparingly for prolonged periods. Other antibiotics include moxifloxacin or intravenous drugs such as ertapenem. However, the current trend is to reduce the use of long courses of systemic antibiotics given the risks that these treatments imply.

Dapsone and acitretin have been shown to be useful in case series publications when symptoms are mild–moderate. Biological drugs are used in patients in which the previously mentioned treatments fail and those with moderate–severe diseases. To date, only adalimumab and recently also secukinumab are approved for use in HS. Cases refractory to these subcutaneous biologics (adalimumab and secukinumab) can be treated with infliximab, which has the disadvantage of being administered intravenously. Other biologics with less evidence, at the moment, to support improvements in HS include ustekinumab, guselkumab, bimekizumab, risankizumab, and different JAK inhibitors. Finally, surgery may be a curative option in locations that allow it and when performed in good time. Wide excision of HS lesions has a lower morbidity and very good results when the disease is axillary; contrarily, it can be complex and result in a high morbidity in perineal and perianal diseases [19, 20].

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73

Other Immune-Mediated Dermatosis (Lichen Planus, Erythema Multiforme, Toxic Epidermal Necrolysis, Graft-Versus-Host Reaction)

Xavier Bosch-Amate, Priscila Giavedoni,
and Cristina Carrera

Abstract

There are several immune-mediated lichenoid/interface dermatoses, with peculiar clinical-pathological findings and a wide range of severity. Occasionally, they can present with some overlap findings that can lead to a challenging differential diagnosis. Lichen planus is a common idiopathic inflammatory disease characterized by intensely itchy, polygonal, violaceous papules. Erythema multiforme is a self-limiting mucocutaneous reaction marked by targetoid lesions that typically affect acrofacial sites, often occurring after infection with the herpes simplex virus. Stevens-Johnson syndrome and toxic epidermal necrolysis are two rare and potentially life-threatening severe cutaneous adverse drug reactions. Graft-versus-host disease is a multi-organ disorder resulting from the transfer of foreign donor hematopoietic stem cells into a host through an allogeneic bone marrow transplant, posing a significant risk of morbidity and mortality in hematological patients. In all cases, a thorough physical examination is crucial, and in many instances, a skin biopsy demonstrating the lichenoid or interface dermatitis is necessary for diagnostic confirmation.

Lichen Planus

Lichen planus (LP) is an idiopathic inflammatory disease of the skin, hair, nails, and mucous membranes mediated by cytotoxic CD8+ T cells. Skin manifestations are characterized by intensely pruritic polygonal violaceous papules or plaques on the extremities and asymptomatic whitish plaques on the mucosae. Most patients only require topical treatments with spontaneous remission after 1 year [1].

Cutaneous LP has an estimated incidence of 1%, whereas asymptomatic oral lesions are estimated to be present in up to 1–4% of the population. Classically, it is predominantly observed in middle-aged adults, but children and the elderly could be affected. Current knowledge suggests that LP is associated with (1) immune dysregulation consistent in activated cytotoxic CD8 T cells against basal keratinocytes; (2) viral infections such as hepatitis C virus, varicella zoster, and human herpesvirus-6 and herpesvirus-7; (3) genetic associations in some HLA alleles; (4) and some environmental risk factors as multiple drugs (angiotensin-converting enzyme inhibitors, thiazide diuretics, antimalarials, quinidine, immunotherapy, among others), vaccinations, psychological factors, or the exposure to some substances as dental restorative materials. Idiopathic LP can be hardly differentiated from lichenoid drug eruptions, which will be a kind of cutaneous adverse reaction directly related to the intake of the drug (Fig. 73.1) [1–4].

Clinical Findings

LP can be classified into multiple clinical variants according to the morphology and kind of primary lesions (annular, linear, atrophic, bullous, erosive, hypertrophic, inverse (folds), lichen planopilaris, mucous or pigmented) but typically presents as a papulosquamous eruption with flat-topped, violaceous, papular lesions of varying size and confluent in well-demarcated plaques (Fig. 73.1). Clinical presentation is often described using the “six P’s” (purple, pruritic, polygo-

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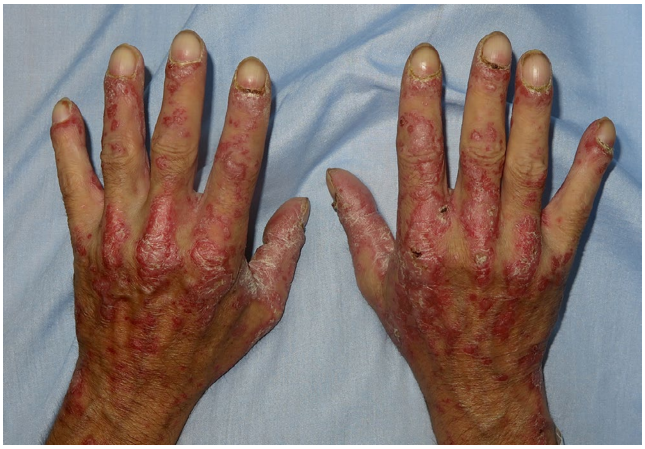

Fig. 73.1 Lichen planus–like induced by drugs. Identical features could be presented in idiopathic LP. Symmetrical violaceous and scaly coalescing papules and plaques on the dorsum. Intense pruritus and nail involvement are shown

nal, planar, papules, and plaques). Another common finding is the presence of Wickham's striae, white reticular lines located on the violaceous papules and plaques. In mucous membranes, the most frequent finding is the presence of reticular whitish lines on bilateral buccal mucosa. Malignant transformation of longstanding erosive oral LP is possible, so the WHO has defined oral LP as a "premalignant condition." Lichen planopilaris is the variant that affects the scalp destroying the hair follicle and leaving irreversible scarring alopecia [1–5].

Diagnosis

Although cutaneous and mucous membrane LP can be clinically diagnosed by experienced dermatologists, a cutaneous biopsy specimen is useful to confirm the clinical diagnosis. Despite its different clinical manifestations, LPs have a characteristic histological pattern with hyperkeratosis without parakeratosis, focal increases in the granular cell layer, irregular acanthosis with a "sawtooth" appearance, vacuolar degeneration of the basal cell layer, and a dense band-like lymphocytic infiltrate at the dermal-epidermal junction. Apoptotic keratinocytes (Civatte bodies) are present in the basal epidermis and superficial dermis. A lesional biopsy for direct immunofluorescence microscopy can be useful, especially when trying to differentiate LP from other autoimmune interphase dermatitis (such as lupus or dermatomyositis) revealing granular deposits of IgA, IgM, IgG, C3, or fibrinogen mixed with apoptotic keratinocytes. Currently, there are no definite diagnostic criteria for lichen planus, so the clinicopathological correlation is the keystone for diagnosis [1].

It is important that, when we evaluate a suspected case of LP, a systematic drug history and clinical history must be performed. Also, ask for symptoms suggestive of the involvement of other locations (such as oral or genital erosions, dysphagia, alopecia, or nail alterations), and physical examination should comprehensively look for clinical signs at the scalp, oral cavity, genitalia, and nails. Other risk factors as hepatitis C virus infections must be explored.

Management

LP can present with a chronic course and/or recurrent flare-ups. Spontaneous remission of cutaneous LP has been observed in up to two-thirds of patients after 1 year, but most patients need some treatment during the disease. Mucous membranes, nails, and follicular LPs are less likely to resolve spontaneously and usually require systemic treatment. Well-described therapies for LP include topical, intralesional, and systemic corticosteroids, systemic retinoids, phototherapy with ultraviolet radiation, topical calcineurin inhibitors, and antimalarials. A combination of therapies and systemic immunosuppressive agents is needed for severe or treatment-resistant cases, including new strategies as biological treatments under investigation [1–5].

Key Features of LP

- Polygonal purple papules and plaques on skin
- Whitish reticular plaques on mucosae
- Intense pruritus
- Can affect any epithelia: skin, mucosa, nails, and hairy areas
- Rule out drug-related LP-like eruptions

Erythema Multiforme

Erythema multiforme (EM), also called polymorphic erythema, is an acute and self-limited mucocutaneous reaction characterized by targetoid lesions especially affecting acrofacial sites. The most common trigger is concomitant or recent herpes simplex virus infection.

EM affects typically young adults and adolescents, with a slight male preponderance, but without racial predilection. The pathogenesis remains elusive, but it is thought that EM consists of an immune reaction triggered by a precipitating factor (especially infections) in certain predisposed individuals. In 90% of cases, the trigger is an infection, being herpes simplex virus, *Mycoplasma pneumoniae, and recently COVID-19,* the most frequently associated. Importantly also, drugs (NSAIDs, antibiotics, allopurinol, lamotrigine, carbamazepine) and systemic diseases can be the associated cause [6–9].

Clinical Presentation

Classically, two forms of EM are distinguished [8]:

- EM minor. Typical targets (Fig. 73.2) are the common symmetrical lesions on the extensor surfaces of extremities and face, although papular atypical targets can be observed. Mucosal involvement is absent or mild, and general symptoms are absent.
- EM major. Typical targets are the common symmetrical lesions on the extensor surfaces of extremities and face, although papular atypical targets and bullous lesions can be also observed. Mucosal involvement is severe, with affectation of lips, oral, and genital mucosae (Fig. 73.3a). Fever and arthralgias are usually present.

In both cases, the body surface area affected is <10%, and the progression to toxic epidermal necrolysis is not possible. The typical target lesions consist of three sharply demarcated components formed by two concentric rings around a central epidermal lesion formed by a bulla or a crust (Fig. 73.2) [6].

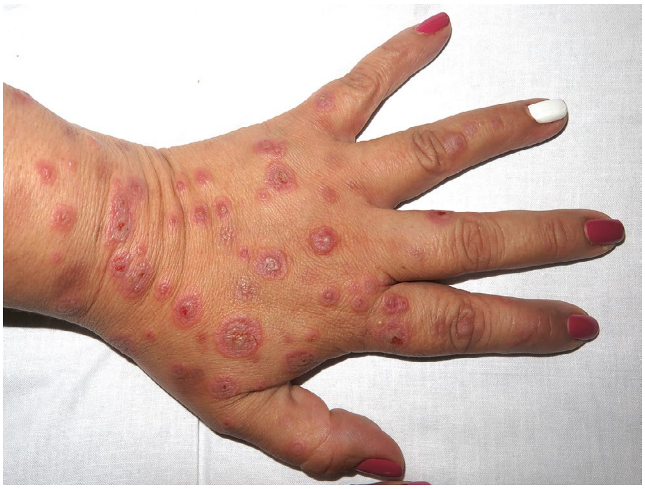

Fig. 73.2 Typical targetoid lesions on the dorsum of hands in erythema multiforme

The onset of the dermatosis is abrupt and acute, with a full development within 72 h and complete healing without sequelae in 2 weeks. Individuals with recurrent HSV-associated EM have several episodes a year, while patients with other triggers may not have flares for years.

Erythema multiforme belongs to the spectrum of clinical presentation that includes the most severe cases of EM major that can overlap with Stevens-Johnson's syndrome and toxic epidermal necrolysis (SSJ/TEN) where mucosal involvement is the rule (Fig. 73.3a) (see next section) [6–9].

Diagnosis

Besides the clinical findings, the suspected diagnosis of EM should always be confirmed by biopsy and immunofluorescence studies. Histological features of EM depend on the time point of biopsy during the disease course. The main findings are the apoptosis of individual basal keratinocytes, mild spongiosis, and interface dermatitis with a lymphocytic infiltrate. Immunofluorescence biopsy shows granular deposits of IgM and C3 around superficial blood vessels and focally at the dermal-epidermal junction. There are no established diagnostic criteria, so EM is a clinicopathologic diagnosis.

There are some conditions that can mimic EM targetoid lesions, including annular urticaria, subacute cutaneous lupus erythematosus, fixed drug eruptions, Sweet syndrome, Kawasaki disease, *erythema annulare centrifugum*, polymorphous light eruption, paraneoplastic pemphigus, bullous pemphigoid, and several forms of vasculitis. Skin biopsy is helpful in ruling out all these diseases. We would like to highlight the term *Mycoplasma*-induced rash and mucositis (MIRM), a clinical EM variant with important mucous affectation (ocular, oral, and genital) in contrast to mild cutaneous involvement [6–9].

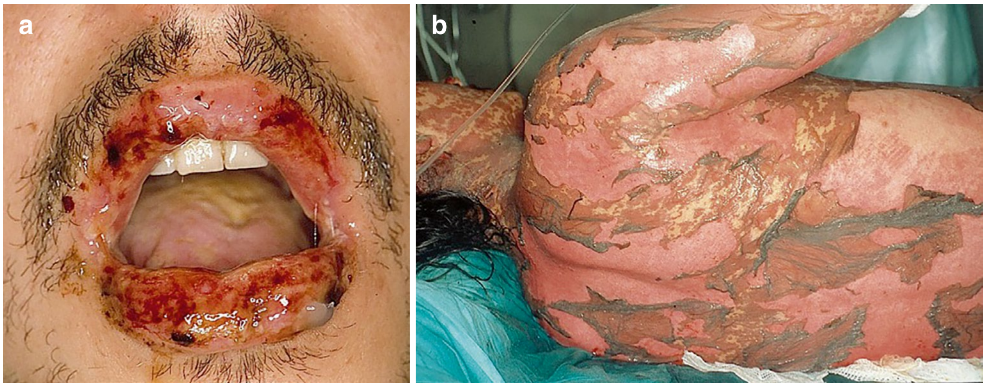

Fig. 73.3 Clinical spectrum of SSJ/TEN: (**a**) erosive cheilitis and mucosal involvement in Stevens-Johnson's Syndrome/erythema multiforme major. (**b**) Extensive necrosis and detachment of the full epidermis in toxic epidermal necrolysis

Management

Most cases of EM minor only need symptomatic treatment with topical antiseptics, topical corticosteroids, and oral antihistamines. In EM major cases, systemic corticosteroids (prednisone 0.5 mg/kg/day for 3–5 days) should be considered after withdrawal of the trigger drug, in such case. Treatment of mucosal lesions includes local anesthetic and antiseptic solutions for oral lesions and topical ophthalmic preparations for ocular lesions. When an infectious precipitating factor can be identified (HSV or *M. pneumoniae*), specific therapy should be initiated. Especially important for those recurrent HSV-associated EM cases in which oral suppressive anti-viral treatment (acyclovir, valacyclovir, famciclovir) can be useful to prevent new flares [6–9].

Stevens-Johnson's Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson's syndrome (SJS) and toxic epidermal necrolysis (TEN) are two rare, potentially life-threatening, severe cutaneous adverse drug reactions (also called SCAR). The average mortality rate is up to 1–5% for SJS and 25–35% for TEN, where optimal management requires early suspicion, immediate discontinuation of the potential causative drug, and rapid initiation of supportive care [10–12].

SJS and TEN are considered different dermatoses of a common spectrum, being only distinguished by their increasing severity. SJS and TEN annual incidences are between one and five cases per million. The incidence of SJS/TEN is much higher among HIV-infected individuals and patients with active cancer than in the general population. Although it is generally considered an adverse reaction to drugs, a non-depreciable number of cases cannot be drug-related. Especially in younger patients (before 18 years of age), viral infections are an important trigger. Main related drugs include allopurinol, carbamazepine, lamotrigine, phenobarbital, phenytoin, antibiotics (especially sulfonamides and cephalosporins), nevirapine, and some NSAIDs such as meloxicam and piroxicam. Recently, antineoplastic target therapies, such as tyrosine kinase inhibitors, EGFR inhibitors, and checkpoint inhibitors, have also been related [10–12].

Current knowledge suggests that SJS-TEN are initiated in certain predisposed people by an altered immune response to an antigenic complex formed by some drug metabolites with certain host tissues. The mechanism of exfoliation and skin necrolysis is cellular apoptosis mediated by activated CD8+ cells, cytotoxic secretory protein granulysin, and interaction of the death receptor-ligand pair Fas-FasL. Population studies have related some HLA polymorphisms with specific drugs, e.g., HLA-B*15:02 in Asians and East Indians who are exposed to carbamazepine and HLA-B*58:01 in Han Chinese exposed to allopurinol [10–12].

Clinical Findings

Clinically, SJS and TEN belong to the same spectrum, and the initial presentation can be quite similar. Dusky-red atypical targetoid confluent macules or morbilliform rash that rapidly evolve to areas with epidermal detachment, erosions and bullous lesions, and severe mucosal involvement in 90% of patients, usually at two or more distinct sites (oral, ocular, pulmonary, genitourinary, gastrointestinal, and genital). The natural history of the disease tends to induce the complete necrosis of the whole epidermis within days. The classical differential fact between SSJ and TEN is the body surface area (BSA) affected by skin detachment: SJS <10% of BSA affected, while TEN has >30% (Fig. 73.3b). When BSA is affected between 10% and 30%, an overlap SJS/TEN is considered. Nikolsky's sign is characteristically positive (achieve skin detachment doing a tangential mechanical mild pressure with the finger over erythematous skin). Some prodromes of fever, anorexia, pharyngitis, and conjunctivitis can be detected a few days before the onset of skin symptoms [10–12].

Diagnosis

Early detection and management are of vital importance for these patients. The diagnosis of SJS-TEN is based on both clinical presentation and histologic findings, so a skin biopsy specimen is recommended in all cases to rule out other erosive-bullous dermatoses. The differential diagnosis TEN includes staphylococcal scalded skin syndrome, drug-induced linear immunoglobulin A dermatosis, generalized bullous fixed drug eruption, acute graft-versus-host disease, acute generalized exanthematous pustulosis (AGEP), cutaneous lupus erythematosus, drug reaction with eosinophilia and systemic symptoms (DRESS), and an infectious generalized morbilliform eruption. Table 73.1 summarizes the diagnostic features [10–13].

Since mortality rates can be up to 30% in TEN, having a prognostic score can be useful. SCORTEN (severity score of toxic epidermal necrolysis) assesses the patient's prognosis (Table 73.2). Morbidity is also important, with a high number of long-term sequelae (cutaneous scarring, irreversible corneal damage, dyspigmentation, dental complications, genitourinary problems, and pulmonary disease) [14].

Table 73.1 Diagnostic features of SJS-TEN

Clinical features
Constitutional symptoms: fever, malaise, anorexia, and pharyngitis
Erythematous, dusky, violaceous macules, morbilliform, or atypical targetoid macules starting on the trunk and spreading distally; confluence on face, trunk, and elsewhere: TEN > SJS/TEN overlap > SJS
Manifests in flaccid bullae, epidermal sloughing, and necrosis with gray hue
Exfoliation of the epidermis involving 10% of body surface area for SJS, 10–30% for SJS/TEN overlap, and >30% for TEN
Oral, genital, and ocular mucositis in nearly all patients
Tender skin and painful mucosal erosions
Positive Nikolsky sign
Positive Asboe-Hansen[a] sign
Systemic symptoms always present in SJS/TEN overlap and TEN
Respiratory tract epithelial involvement in 25% of patients with TEN
Histologic features
Full-thickness epidermal necrosis
Subepidermal split, lymphocytic infiltrate at the dermal-epidermal junction, CD41 T cells in the dermis, and CD81 T cells in the epidermis
Endothelial apoptosis

[a] Means the demonstration of the extension of a blister to adjacent unblistered skin when mild pressure is put on the top of the blister

Table 73.2 SCORTEN score for toxic epidermal necrolysis [14]

Factor	**Points**
Age ≥40 years	1
Heart rate ≥120/min	1
Underlying malignancy	1
Skin detachment ≥10% of BSA on day 1	1
Serum urea ≥10 mmol/L (28 mg/dL)	1
Serum bicarbonate <20 mmol/L (20 mEq/L)	1
Serum glucose ≥14 mmol/L (250 mg/dL)	1
Scorten points	**Mortality rate (%)**
0–1	3.2%
2	12.1%
3	35.8%
4	58.3%
≥5	>90%

Management

Optimal medical management of SJS and TEN requires early diagnosis, immediate discontinuation of the suspicious causative drug/s and supportive care in an intensive care unit, burn center, or similar specialized unit. The keystone of the treatment is the prevention of infections and sepsis and the adequate wound management and restoration of the skin barrier. Current literature does not convincingly support the use of adjuvant systemic immunosuppressive therapies, probably depending on the time of instauration and comorbidities of the patient. Different metanalyses have supported the use of cyclosporine 3 mg/kg/day for 10 days to decrease mortality and stop disease progression. Early administration of high doses of intravenous immunoglobulin (IVIG) >2 g/Kg correlated with an increased survival rate and lower mortality rate. Systemic corticosteroids have been a mainstay of therapy for decades, but their use remains nowadays controversial. Recently, TNF-α inhibitors (e.g., etanercept, infliximab) showed promising results [10–12].

Graft-Versus-Host Disease

Graft-versus-host disease (GVHD) is a multi-organ disorder due to the transfer of foreign donor hematopoietic stem cells into a host via an allogeneic bone marrow/stem cell transplant. More rarely, GVHD can be seen following transfusion of non-irradiated blood products (to immunocompromised hosts), by maternal-fetal transmission, or in the setting of solid organ transplantation. It remains an important cause of morbidity and mortality in hematological patients.

Every year, the number of hematopoietic transplants increases so the incidence of GVHD is also worldwide higher. Removal of donor T cells decreases GVHD risk but inversely increases cancer relapse due to the cancellation of donor T-cell graft-versus-tumor effect. Two forms of GVHD are classically described, the acute one (aGVHD) and the chronic one (cGVHD), and the skin is the most commonly and the earliest involved organ in both forms.

In the past, differentiation of aGVHD and cGVHD was linked to the temporal relationship to transplantation (≤ or >100 days); however, nowadays, the distinction is based on clinical-pathological findings [15].

Clinical Findings

Acute GVHD presents in the skin as erythematous macules and papules and initiates 1–2 months after the transplant. Skin manifestations can vary from mild acral morbilliform exanthem to a generalized erythroderma with bullae resembling a TEN. The gastrointestinal tract (nausea, diarrhea, abdominal pain) and the liver (transaminitis, cholestasis, bilirubin elevation) are the two other primary organ systems affected by aGVHD [15].

Unlike aGVHD, cGVHD can affect any system, including eyes (keratoconjunctivitis sicca, blepharitis, corneal erosions), salivary glands (sicca syndrome), lungs (bronchiolitis obliterans), liver (transaminitis, hyperbilirubinemia), esophagus (strictures, webs), heart, bone marrow, muscles, and pancreas (exocrine insufficiency). Based on NIH Consensus Criteria, there are some "diagnostic" mucocutaneous manifestations sufficient to consider cGVHD without other studies [15]:

- Skin: Poikiloderma, lichen planus–like eruption (most characteristic manifestation of cutaneous cGVHD), deep sclerotic features, morphea-like, and lichen sclerosus–like lesions
- Oral mucosa: Lichen planus–like lesions (Fig. 73.4)
- Genital mucosa: Lichen planus–like, lichen sclerosus–like, vaginal scarring, clitoral/labial agglutination (females), phimosis, and scarring/stenosis of the urethral or meatus (males)

There are other "distinctive" mucocutaneous manifestations that require biopsy or laboratory confirmation as well as rule out other possible causes in order to confirm cGVHD diagnosis [15]:

- Skin: Depigmentation (vitiligo), papulosquamous lesions, xerosis and ichthyosis, keratosis pilaris, hypopigmentation, and hyperpigmentation
- Oral mucosa: Xerostomia (dryness), mucocele, mucosal atrophy, ulcers, and pseudo-membranes
- Genital mucosa: Erosions, fissures, and ulcers

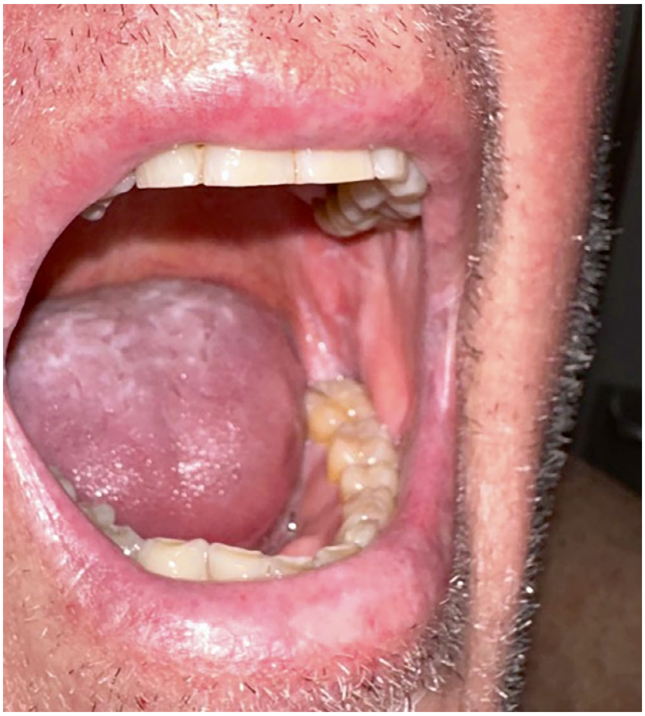

Fig. 73.4 Lichen planus–like oral lesions in chronic GVHD. Note the shiny white plaques on the lips and oral mucosae, reticulated surface is characteristic

- Nails: Longitudinal ridging, nail splitting or brittleness, onycholysis, pterygium unguis, and nail loss
- Hair: Scarring or non-scarring scalp alopecia and loss of body hair, premature graying, thinning, or brittleness

Diagnosis

Histologically, depending on aGVHD grade, we can find widespread keratinocyte necrosis, focal vacuolar changes, dermal lymphocytic infiltrate in the upper dermis, and large areas of separation of the epidermis from the dermis. The histology of cGVHD reflects the variable skin manifestations of the different conditions observed (lichenoid, sclerotic…).

The clinical scoring of mucocutaneous involvement will be done according to a 4-point scale (0–3) with 0 representing no involvement and 3 reflecting severe impairment. Some skin manifestations will be also measured according to the body surface area (BSA).

Acute GVHD differential diagnosis includes basically viral or drug exanthem and engraftment syndrome. Because of its clinical variability, the differential diagnosis of cGVHD is broader and includes lichenoid drug eruptions, autoimmune connective tissue diseases (lupus, dermatomyositis, morphea, systemic sclerosis), and papulosquamous disorders. In both cases, the antecedent of a bone marrow transplant is a clue for the correct diagnosis [15].

Management

GVHD should be managed in a coordinated multidisciplinary team. Mucocutaneous treatment of aGVHD consists of topical and systemic corticosteroids with other immunosuppressants as calcineurin inhibitors (tacrolimus, cyclosporine). In recalcitrant cases, other immunosuppressive agents such as mycophenolate mofetil and TNF-α antagonists are frequently needed. First-line cGVHD treatment is based on topical and systemic corticosteroids. For more severe cases, combination with other drugs is needed to avoid irreversible scarring and functional impairment—hydroxychloroquine, mycophenolate mofetil, imatinib, rituximab, acitretin, or extracorporeal photophoresis. Ruxolitinib (JAK inhibitor) is approved by the FDA and EMA in adult and pediatric patients 12 years and older with acute or chronic GvHD after the failure of one or two lines of systemic therapy [15].

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Part IX

Cardiovascular and Pulmonary Autoimmune Diseases

Autoimmune Dilated Cardiomyopathy

74

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Abstract

Dilated cardiomyopathy (DCM) is a prevalent and complex heart condition characterized by the dilation and impaired contractility of both left and right ventricles, often leading to heart failure and transplantation. While some cases of DCM are associated with acute and chronic inflammation, idiopathic DCM is diagnosed after ruling out secondary causes (genetics, infections, toxins, and autoimmune conditions). Autoimmune factors play a significant role in the pathogenesis of DCM, particularly in cases of autoimmune DCM (ADCM). Antibodies targeting mitochondrial proteins and cardiac myosin, complement activation, and cytokines contribute to myocardial damage. Clinical manifestations of DCM typically present as heart failure symptoms, including palpitations, chest pain, and shortness of breath. Here, we propose a diagnosis criterion for ADCM. Patients with established ADCM will gain the greatest beneficial effect of immunosuppressive and immunomodulating treatment.

Keywords

Dilated cardiomyopathy (DCM) · Autoantibodies · Left ventricular end-diastolic volume (LVEDV) · Anti-a-myosin heavy chain · Anti-b1 adrenergic receptor

Dilated cardiomyopathy (DCM) is the most frequent cause of heart failure and transplantation [1]. It is characterized by dilatation and contractile dysfunction of the myocardium of both left and right ventricles, with no other abnormal preload and afterload abnormalities [2–4].

In some patients, myocarditis and DCM are acute and chronic phases of an inflammatory process [5]. Idiopathic DCM is diagnosed after excluding secondary causes such as genetic factors, familial presentation, infections (usually viral agents), toxins or chemotherapeutic drugs, metabolic abnormalities, nutritional deficiencies, neuromuscular diseases, and inflammatory conditions [3, 4, 6].

Several predisposing conditions may coexist, along with immune abnormalities and autoantibodies that play a crucial role in the pathogenesis [7, 8]. Autoimmunity may be triggered by various exogenous factors in predisposed individuals [8]. DCM may also emerge in autoimmune rheumatic disorders such as systemic sclerosis, systemic lupus erythematosus (SLE), dermatomyositis, and eosinophilic granulomatosis with polyangiitis (EGPA) [3, 4, 6].

The pathogenesis of DCM is yet unclear. In the case of autoimmune DCM (ADCM), antibodies to adenosine diphosphate (ADP) and ATP mitochondrial translocator protein have been shown to cause cell lysis in rats [8]. Anti-cardiac myosin is also assumed to be an essential mediator in the progression of the disease [8]. Complement activation following antibody deposition causes myocardial damage,

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and a local increase in TNFa, nitric oxide, mitogen-activated protein kinases (MAPKs), and cytokines damages the cardiac tissue [8]. Other antibodies associated with ADCM are the β1-adrenergic receptor, muscarinic acetylcholine receptor M2, and cardiac myosin. These antibodies have been found in up to 60% of patients. Some studies have shown cell infiltration, HLA ll expression, and adhesion molecules in the cardiac tissue [4].

Epidemiology

The prevalence of DCM is estimated to be 1 in 250 people, and the incidence of 1 in 500 individuals [1]. The reported prevalence of idiopathic DCM in the USA is 36 cases per 100,000 persons and an annual incidence of 5–8 new cases for the same population size [6, 9]. In the USA, 9000 deaths are attributed to DCM annually and 403,000 deaths worldwide, meaning 5.9 per 100,000 people [4, 10].

Clinical Manifestations

Preliminary signs and symptoms usually begin between ages 20 and 50 years, although people of all ages might be affected [6]. The common manifestations are symptomatic heart failure (up to 95% of cases), usually with severe cardiac dysfunction, palpitations, chest pain, and dyspnea on exertion [11]. Systemic and pulmonary embolism are less common, and asymptomatic cardiomegaly may also occur (Table 74.1) [6]. Both supraventricular and ventricular tachyarrhythmia may arise, but it is uncommon for syncope or sudden death to be the initial presenting symptom [6]. The mortality rate is as high as 15–50% in 5 years, primarily because of ventricular arrhythmias and heart failure [9].

Table 74.1 Symptoms and signs of autoimmune dilated cardiomyopathy

Symptom	Percentage
Left and right heart failure symptoms	
Initial presentation	75–85
Overall	95
Dyspnea on exertion	86
Palpitations	30
Peripheral edema	29
Asymptomatic cardiomegaly	4–13
Chest pain on exertion	
Initial presentation	8–20
Overall	35
Systemic and pulmonary embolism	1.5–4

Laboratory Findings

Electrocardiography

The ECG recording might be normal or present T-wave changes and Q waves in cases of extensive fibrosis. Also, repolarization abnormalities or conduction disturbances such as PR prolongation, AV blocks, left bundle branch block (LBBB), and hemiblock can be found. Tachyarrhythmias, particularly atrial fibrillation, are common and may suggest the development of left ventricular reverse remodeling (LVRR), associated with an unfavorable prognosis [3, 11].

Pathological Features

Histologically, cellular hypertrophy, myocyte degeneration, interstitial fibrosis, and small clusters of lymphocytes may be present [6, 10]. The heart muscle stains positive for complement membrane attack complex C5b-9, indicating that the complement system has a role in the pathogenesis [12]. Loss of intracellular cardiac myofilaments is associated with mortality [6]. Other morphological alterations include vacuole formation, cardiomyocyte hypertrophy, myocytolysis, scar formation, granulomas, and giant cells [4].

Serological Features

Heart-specific autoantibodies may be found in about a third of patients, including anti-a-myosin heavy chain, anti-b1 adrenergic receptor, and anti-mitochondrial antigens such as adenine nucleotide, translocator, branched-chain ketoacid dehydrogenase, and M7 adenosine diphosphate-adenosine triphosphate carrier protein (Table 74.2) [5, 6]. Some autoan-

Table 74.2 Serological circulating autoantibodies in dilated cardiomyopathy and normal subjects

Antibody	Prevalence in DCM (%)	Healthy
Inhibiting anti-b1 receptor	30–31	4–12
Stimulating anti-b1 receptor	95	0
Anti-b myosin heavy chain	44	2.5
Anti-a-myosin heavy chain	20	2
Anti-M7	31	0
Anti-M2 receptor	39	7.5
Adenine nucleotide translocator	57	0
BCKD-E2	60	0
Anti-sarcolemmal antibody	10	25
Anti-myolemmal antibody	9	12
Anti-fibrillary antibody	24	6
Anti-interfibrillary	41	3

BCKD-E2 branched-chain a-ketoacid dehydrogenase dihydrolipoyl transacylase tibodies mentioned in the table are absent or not as commonly found in healthy subjects but may be disease and organ nonspecific [5].

Diagnostic Criteria

The most practical diagnostic procedure is echocardiography, although radionuclide scanning or angiography might also be used to confirm the diagnosis [9]. Left ventricular dilatation, segmental or global hypokinesis, and reduced ejection fraction are present [6]. Fulfillment of echocardiographic diagnostic criteria (Table 74.3) requires an ejection fraction smaller than 45% and fractional shortening smaller than 25%. Also, it requires a left ventricular end-diastolic dimension that exceeds 112% than expected according to age and body surface area. A cutoff of 117% was proposed to increase sensitivity in family members [3, 7]. Affected first-degree relatives can be diagnosed in the presence of cardiac dilatation without systolic dysfunction if one minor criterion is present. The presence of three minor criteria without fulfilling the major criteria can also establish the diagnosis in suspected familial presentation (Table 74.4) [9]. Diagnosis requires excluding other causes of systolic dysfunction, hypertension greater than 160/100 mmHg, coronary artery disease (with >50% obstruction in a major artery), chronic alcohol abuse, sustained supraventricular tachycardia, systemic disease, pericardial or congenital heart disease, and cor-pulmonale [9].

Table 74.3 Echocardiographic criteria of dilated cardiomyopathy

Fulfillment of both criteria
1. Ejection fraction <45% and fractional shortening <25% 2. Left ventricular end-diastolic dimension (LVEDD) >112% than expected according to age and body surface area. Cutoff of LVEDD. >117% is preferred in familial presentation
Exclusion criteria
1. Blood pressure >160/100 mmHg 2. Intravascular obstruction of the main coronary artery lumen exceeds 50% 3. Alcohol intake >80 g/day for males or >40 g/day for females 4. Persistent supraventricular tachyarrythmias 5. Systemic disease 6. Pericardial disease 7. Congenital heart disease 8. Cor-pulmonale

Endomyocardial biopsy may be required to exclude myocarditis, although it has a limited therapeutic effect [6]. DCM cannot be solely attributed to autoimmunity; no criteria are currently available to define pure ADCM. Hence, we propose a new criteria system for diagnosis of ADCM (Table 74.5). The new criteria are based on establishing the autoimmune basis of the disease [13] following an echocardiographic diagnosis. Establishing the diagnosis of ADCM requires fulfilling two major echocardiographic criteria and at least one minor criterion. The proposed minor criteria are as follows: (a) proven mononuclear cell infiltrate with abnormal human leukocyte antigen (HLA) presentation; (b) circulating anti-heart autoantibodies or autoreactive lymphocytes in patients and unaffected family members; (c) in situ evidence of autoreactive lymphocytes and/or autoantibodies in cardiac tissue; (d) disease induction in animal following transfusion of the patient's serum, antibodies, or lymphocytes; and (e) proven clinical or echocardiographic improvement following immunoadsorption or immunosuppressive therapy. This new proposed entity has a possible therapeutic significance because we assume that patients with established ADCM will gain the greatest beneficial effect of immunosuppressive and immunomodulating treatment. The proposed criteria are based on the evidence that autoimmunity has a vital role in the pathogenesis. Known autoimmune association includes mononuclear and T-lymphocyte infiltration and HLA class II upregulation on cardiac endothelium, circulating and in situ autoantibodies, known autoantigens, familial aggregation, and existence of other familial autoimmune diseases, weak HLA DR4 association, and a possible clinical course with exacerbation and remissions [3, 12, 14, 15]. Additional indirect proof of autoimmunity is found by

Table 74.4 Echocardiographic criteria of familial dilated cardiomyopathy

Major criteria
1. Defined criteria for dilated cardiomyopathy (as stated above)
Minor criteria
1. Unexplained supraventricular (atrial fibrillation or sustained arrhythmias) or ventricular arrhythmias, frequent >100/24 h or repetitive (three or more beats with >120 beats/min before the age of 50 years 2. Left ventricular dilatation >112% of the predicted value [29] 3. Left ventricular dysfunction: ejection fraction <50% or fractional shortening <28% 4. Unexplained conduction disease: II or III atrioventricular conduction defects, complete left ventricular bundle branch block, and sinus nodal dysfunction 5. Unexplained sudden death or stroke before 50 years of age 6. Segmental wall motion abnormalities (<1 segment or one if not previously present) in the absence of intraventricular conduction defect or ischemic heart disease
Affected
Presence of the major criteria (left ventricular dilatation and systolic dysfunction) • Or left ventricular dilatation (>117%) + one minor criterion • Or three minor criteria
Unknown
• Presence of one or two minor criteria

Table 74.5 Proposed diagnosis criteria of autoimmune-mediated dilated cardiomyopathy

Major
1. Fulfillment of echocardiographic criteria of dilated cardiomyopathy 2. Excluding secondary cardiac injury because of infections, alcohols, toxins or chemotherapeutic drugs, metabolic abnormalities, nutritional deficiencies, neuromuscular diseases, or collagen vascular disorders
Minor
1. Proven mononuclear cell infiltrate with abnormal human leukocyte antigen (HLA) presentation 2. Circulating anti-heart autoantibodies or autoreactive lymphocytes in patients and unaffected family members 3. In situ evidence of autoreactive lymphocytes and/or autoantibodies in cardiac tissue 4. Disease induction in animals following transfusion of the patient's serum, antibodies, or lymphocytes 5. Proven clinical or echocardiographic improvement following immunoadsorption or immunosuppressive therapy
Supporting evidence but not considered criteria
1. Clinical course of exacerbation and remissions 2. Positive HLA-DR4 3. Familial clustering of autoimmune diseases and family history of dilated cardiomyopathy (two or more affected individuals or sudden cardiac death in a first-degree relative younger than 35 years)
• *Diagnosis requires two major and at least one minor criteria*

disease induction following the transmission of anti-myosin CD4 T cells from mice with myocarditis to SCID mice [12]. Induction of experimental disease and autoimmune response in animals after immunization with cardiac-type a-myosin has also been proven [5, 12, 16].

Diagnosis of ADCM is based on establishing its autoimmune basis. Yet there is partial direct evidence of autoimmunity in DCM because it has never been attempted to induce the disease by directly transferring autoantibodies in humans. Moreover, a review of the relevant medical literature revealed no report of trans-placental transmission of immunoglobulins and secondary disease induction in newborns. Nevertheless, many other acknowledged autoimmune diseases have partial or no direct proof of their autoimmune basis [13]. The greatest pitfall of the proposed criteria is the limited practical use of some minor diagnostic criteria, mainly because of the need for invasive biopsy or the required complex special laboratory exams.

Prediction of Onset

DCM commonly appears in familial clusters, and mild dilatation without systolic dysfunction may be found in 9–21% of asymptomatic relatives. This may represent early disease manifestation [6]. Cardiac-specific autoantibodies increase the risk of future DCM [6]. Echocardiography and anti-heart antibody screening in asymptomatic relatives can identify high-risk patients. The positive predictive value (PPV) of echocardiographic screening is 10%, anti-heart antibody screening is 7%, and combined PPV rises to 18% [7]. Negative anti-heart antibodies have a negative predictive value of 98% over a 5-year follow-up period [7].

Prognosis

Prognosis is poor for symptomatic patients, and most of the deaths are caused by the progression of heart failure [6]. Spontaneous partial remission may be found in 20–45% of patients, usually shortly after initial symptoms. Severe cardiac dilatation and dysfunction usually mean a worse prognosis. Other indications for poor prognosis include right ventricular dilatation and failure, global ventricular dysfunction, a spherical shape of the left ventricle, syncope, S3 heart sound, systemic hypotension, and pulmonary hypertension [6].

Therapy and Prevention

Lifestyle changes, including weight loss and refraining from smoking or consumption of alcohol, should be advised to all patients. Moderate physical activity is beneficial, and dietary recommendations are the same as for other causes of heart failure [6]. Symptomatic patients should be treated with diuretics, vasodilators such as ACE inhibitors, hydralazine, nitrates, digitalis, and beta-blockers [6, 8]. Nevertheless, diuretics should not be considered monotherapy because they potentially contribute to disease progression [3]. Beta-blockers possibly eliminate the effect of stimulatory anti-b1 receptor antibodies [5]. Patients with severe left ventricular dysfunction, atrial fibrillation, history of thromboembolism, and evidence of intracardiac thrombus should be treated with warfarin [3, 6]. Despite this medical therapy, the prognosis remains poor, and definite treatment often requires heart transplantation [8]. Although there is a high risk of sudden cardiac death, class I antiarrhythmic agents have paradoxically caused increased mortality. Amiodarone usage has shown conflicting results [3]. Automatic cardioverter-defibrillator may be beneficial for selected patients [6].

Although autoimmunity plays a role in pathogenesis, prednisone has shown disappointing therapeutic effects [6]. Treatment with prednisone and azathioprine in selected patients has shown echocardiographic and clinical improvement despite no change in hospital admissions and death rates [17]. Immunoadsorption has eliminated circulating autoantibodies such as anti-b1 adrenergic receptors. Moreover, further application of IgG substitution has increased contractile indexes [8] and decreased HLA class II expression and lymphocyte infiltration in the myocardium [2]. Intravenous immunoglobulin therapy has failed to improve cardiac function in controlled trials [8, 18]. The only definite treatment for advanced heart failure is cardiac transplantation.

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75

Rheumatic Fever

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Abstract

Rheumatic fever (RF) is an inflammatory condition involving the heart, joints, skin, and brain that emerges following group A streptococcal infection. The use of appropriate diagnostic criteria for RF is crucial to not underdiagnose this frequent condition that carries the risk of significant long-term morbidity. The most frequent and severe manifestation of RF is carditis. Echocardiography detects subclinical carditis in many patients lacking any clinical presentation, up to 10 times more than cases having clinical evidence of disease. This chapter emphasizes the significance of the Jones criteria, revised over the years, in diagnosing RF, especially in high-risk populations, and the benefit of echocardiography.

Keywords

Rheumatic fever · Echocardiography · Jones criteria

Introduction

Rheumatic fever (RF) is a systemic inflammatory condition affecting the peri-arteriolar connective tissue following a group A streptococcal infection [1]. Molecular mimicry between streptococcal and human proteins is the triggering factor leading to autoimmunity in RF and rheumatic heart disease (RHD); nevertheless, some evidence has shown that group C and G *Streptococcus* also contributes to the pathogenesis of RHD. Some other hypotheses for the pathogenesis are collagen-associated neoantigens, epitope spreading, and T-cell receptor degeneration [2]. Several HLA class II alleles are associated with the disease, mainly HLA-DR7. Cardiac myosin is one of the significant autoantigens involved in rheumatic heart lesions, and several peptides from the light meromyosin region were recognized by peripheral and intralesional T-cell clones from RF and RHD patients [1, 2]. This syndrome has been linked to other genetic factors thanks to the Human Genome Epidemiology Network (HuGENet), in which single nucleotide polymorphisms (*TGFB1* and *IL1B*) were associated with a higher risk of RHD [3].

Infection with group A *Streptococcus* (Strep A) is estimated to cause over 500,000 deaths per year, most of which are related to RF and RHD [4]. The antiphagocytic bacterial surface M protein is a significant candidate antigen in the development of RF and also in the development of a vaccine to prevent RHD. Major obstacles in developing an M protein–based vaccine are the widespread diversity of circulating streptococcal strains and M protein types and the possibility of inducing autoimmunity following vaccination due to molecular mimicry between the M protein and host tissue proteins [4]. Nevertheless, previous studies demonstrate that the total IgG antibodies to M protein had no association with a following infection with Strep A, and only 12.5% of patients develop type-specific antibodies after the infection. Some antibodies against antigens that promote opsonophagocytosis or inhibit virulence are being studied as candidates for the Strep A vaccine [5, 6].

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Diagnostic Criteria

As a worldwide disease, RF has well-known diagnostic criteria named after Dr. Jones. These criteria were revised in 2015 by the American Heart Association (AHA) with some modifications that responded to new technological advances and increased sensitivity, mainly in high-risk populations [6]. RF is a condition carrying possible long-term morbidity and necessitating long-term therapy; therefore, these diagnostic criteria should be judged whether they overdiagnose or, more importantly, underdiagnose RF. The Jones criteria underwent several modifications over the years, and going over the five revisions made after the original Jones criteria, it seemed that modifications of these criteria were primarily corrective and perfective [6, 7]. In 2020, the last Australian guidelines were published with some changes to their criteria for RF according to the latest evidence; in low-risk populations, subclinical carditis was taken as a major criterion, and in the same people, erythrosedimentation rate (ESR) >60 mm and fever >38.5 °C were minor criteria and another change was to take a previous history of RF and two major or one major and two minor or three minor criteria for a definite recurrent episode of RF [8]. The revised Jones criteria from the AHA 2015 are shown in Table 75.1.

Table 75.1 Revised Jones criteria for acute rheumatic fever

	Low-risk population	High-risk population	
Major criteria			
Carditis	Clinical or subclinical	Clinical and subclinical	All layers of cardiac tissue are affected (pericardium, epicardium, myocardium, and endocardium). The patient may have a new or changing murmur, with mitral regurgitation being the most common, followed by aortic insufficiency. Subclinical: echocardiographic evidence of valvulitis
Polyarthritis	Polyarthritis only	Monoarthritis or polyarthritis Polyarthralgia	This is a migrating arthritis that typically affects the knees, ankles, elbows, and wrists. The joints are painful, and the symptoms are responsive to anti-inflammatory medicines Polyarthralgia is considered after excluding other causes
Chorea	Present	Present	This is also known as Sydenham's chorea, or "St. Vitus' dance." There are abrupt, purposeless movements. This may be the only manifestation of RF, and its presence is diagnostic. It may also include emotional disturbances and inappropriate behavior
Erythema marginatum	Present	Present	This non-pruritic rash commonly affects the trunk and proximal extremities but spares the face. This rash typically migrates from central areas to the periphery and has well-defined borders
Subcutaneous nodules	Present	Present	Usually located over bones or tendons, these nodules are painless and firm
Minor criteria			
Fever	≥38.5 °C	≥38 °C	–
Arthralgia	Polyarthralgia	Monoarthralgia	
Acute phase reactants	ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dL	ESR ≥30 mm/h and/or CRP ≥3.0 mg/dL	ESR: erythrocyte sedimentation rate CRP: C-reactive protein
Prolonged PR interval	Considering age variations	Considering age variations	–
Evidence of preceding streptococcal infection: any of the following is considered adequate evidence of infection: 1. Increased antistreptolysin O or other streptococcal antibodies 2. Positive throat culture for group A b-hemolytic streptococci 3. Positive rapid direct group A *Streptococcus* carbohydrate antigen test			
Initial RF: two major criteria or one major plus two minor criteria			
Recurrent RF: two major criteria or one major and two minor criteria or three minor criteria			

Clinical Presentation

The description of the clinical and demographic characteristics of RF is complex due to the heterogeneity in different geographic areas [6]. Episodes in Brazil disclosed that there was a predominance of females; in only one-third of the cases was the disease diagnosed at the first episode of RF, and the most frequent clinical manifestations were carditis (69.7%), arthritis (21.4%), and chorea (6.1%) [9]; on the other hand, the AHA reports carditis in 50–70%, arthritis in 36–66%, chorea in 10–30%, and lastly subcutaneous nodules from 0 to 10% and erythema marginatum in less than 6% but with high specificity [6]. Nevertheless, the presentation of these manifestations depends on the studied population; Table 75.2 illustrates this difference according to the Jones criteria.

Before the last 2015 revision, Stewart et al. [12] tested whether the Jones criteria were used appropriately for diagnosing RF. The medical records of patients discharged with a diagnosis of ARF were evaluated, and 32% did not fulfill the Jones criteria. It seemed that the criteria were used appropriately to diagnose initial episodes of RF but less successfully in recurrent episodes [12]. In another study, 35 patients with suspected RF were prospectively studied [13], and 50% had a discharge diagnosis of definite RF, whereas 31% posed diagnostic difficulties due to mild symptoms that failed to fulfill the Jones criteria. Notably, at least 29% of patients without prior recognized RF or RHD had echocardiographic evidence of established RHD, suggesting that previous episodes were missed [13]. These last examples justify the most recent revision of the Jones criteria, giving more weight to echocardiograms and classifying populations as high or low risk [6]. Low risk is defined as an incidence of fewer than two cases per 100,000 children of 5–14 years old per year or RHD prevalence of less than 1 per 1000 people of all ages per year; on the other hand, moderate and high risk are all those who do not accomplish low-risk criteria [6].

Including echocardiographic criteria in the last revision responds to the higher prevalence of echocardiographic confirmed subclinical RHD among high-risk patients. Subclinical RHD is established when rheumatic valvulopathy is found on echocardiographic screening of an asymptomatic patient. As Karthikeyan and Guilherme [14] proposed, subclinical RHD can be used for incidence screening due to the low cost, repeatability, and wide variation of RF. On the other hand, subclinical carditis was added to the criteria and given the same weight as carditis due to the widespread availability of echocardiograms and the declining of auscultation skills [6].

Sydenham's chorea is a neurological manifestation of RF characterized by chorea and neuropsychiatric symptoms. It is associated with neuron-specific antibodies, particularly immunoglobulin G (IgG), which target the basal ganglia, leading to excessive dopamine release from neuronal cells. Its pathogenesis is explained by antibodies resulting from molecular mimicry with Strep A antigens. Binding these antibodies to antigens on neuronal cell membranes, such as lysoganglioside and dopamine receptors, alters cellular biochemistry and signaling through activating calcium/calmodulin-dependent protein kinase type II (CAMK2) [15].

Table 75.2 Clinical manifestations in different populations

Clinical manifestation	Israel Tal R. et al. [10] *n*: 307	Indonesia Lilyasari O et al. [11] *n*: 279	Total *n*: 586
Carditis *n* (%)	160 (52%)	178 (63%)	338 (57%)
Arthritis *n* (%)	197 (64%)	36 (12%)	233 (39.8%)
Chorea *n* (%)	47 (15%)	2 (0.7%)	49 (8.3%)
Subcutaneous nodules *n* (%)	2 (0.7%)	7 (2.5%)	9 (1.5%)
Erythema marginatum *n* (%)	16 (5.2%)	2 (0.7%)	18 (3%)
Fever *n* (%)	94 (32%)	66 (23.6%)	160 (27.3%)
Arthralgias *n* (%)	229 (75%)	33 (11.8%)	262 (44.7%)
Elevated CRP *n* (%)	269 (87%)	59 (21.14%)	328 (56%)
Elevated ESR *n* (%)	278 (91%)	65 ((23.2%)	343 (58.5%)
Prolonged PR interval *n* (%)	23 (7.5%)	6 (2.1%)	29 (5%)

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate

Treatment

The target of RF treatment is eradicating Strep A with penicillin. This goal can be achieved with a dose of benzathine benzylpenicillin or phenoxymethylpenicillin for 10 days. Other options include cephalosporin, amoxicillin, and azithromycin [13]. In the case of chorea and carditis, steroids or IVIg can be considered [14]. Carbamazepine and sodium valproate can be considered in chorea for symptomatic relief [13]. In the case of arthralgias, acetylsalicylic acid (aspirin) for 1–3 days at a dose of 80–100 mg/kg has been found to have a better response than other non-steroidal anti-inflammatory drugs (NSAIDs) [13].

Even though the incidence and prevalence of RF have declined since the introduction of antibiotics, the new diagnostic criteria help include all high- and low-risk patients without symptoms. In the case of high-risk patients, echocardiography may help initiate treatment promptly to reduce complications. Also, it will help us to have a better picture of the epidemiology of RF.

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76

Accelerated Atherosclerosis in Autoimmune Diseases

Sara Monti, Pier Luigi Meroni, and Nicoletta Ronda

Abstract

Atherosclerosis (AS) is a chronic inflammatory disease of arterial vessels, leading to chronic and acute ischemic damage or hemorrhages in virtually any organ. Atherosclerotic plaque formation is the result of inflammatory processes that mediate lymphocyte and macrophage infiltration, lipid intra- and inter-cellular deposition, and eventually smooth muscle cell migration/proliferation and fibrosis. Adaptive and innate immune responses against exogenous as well as self-antigens cooperate in triggering such processes. The atherogenic processes may be magnified and accelerated in patients with autoimmune rheumatic diseases (AIRDs) because of the underlying immune abnormalities, the consequent systemic inflammation and the effects of some concomitant chronic therapies. As a matter of fact, accelerated AS is responsible for increased mortality and morbidity in almost all AIRDs, nowadays. Diagnostic strategies to detect early atherosclerotic lesions and to apply preventive therapeutical approaches have been proposed in order to avoid complications related to accelerated AS in AIRDs.

Keywords

Autoimmune rheumatic diseases · Atherosclerosis · Innate-immunity · Adaptive immunity · Inflammation · Atherothrombosis · Immunomodulating drugs · Diagnosis · Prevention

Pathogenesis

Atherosclerotic plaque is not only derived from the simple deposition of lipids in the subendothelial space but also is the result of complex processes actively involving various cellular and humoral elements of innate and adaptive immunity. Moreover, the established evidence of accelerated AS as the main mechanism leading to an increased cardiovascular risk (CVR) in several rheumatologic disorders, [e.g. systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), antiphospholipid syndrome (APS) in particular if associated with SLE, and systemic sclerosis], together with experimental data point to the role of autoimmunity in the process [1]. In autoimmune diseases, the interaction between chronic systemic inflammation and intimal autoimmune processes with traditional risk factors is particularly relevant. This interplay is further influenced by pharmacologic treatment, in some cases associated with increased CVR as for nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids [1], and in other cases with atheroprotection and reduced CVR as for various DMARDs [2, 3].

In autoimmune rheumatic diseases (AIRD), besides traditional risk factors, other factors contribute to the increased risk of CV complications, especially inflammation and disease activity. Systemic inflammation plays a proatherogenic role by favoring insulin resistance, lipoprotein level and function disturbances, hypercoagulation, endothelial dysfunction, and oxidative stress. Thus, the increased CVR observed in AIRDs is due to a larger plaque burden and higher lesion instability [3].

The pathological process is characterized by lipid deposition in the extracellular space, subendothelial infiltration by lymphocytes and monocytes, activation of vascular smooth muscle cells (VSMCs), responsible for intraplaque microcalcifications, and eventually accumulation of macrophage- and VSMC-derived foam cells. Local chemical modifications (especially oxidation) of lipids, such as low-density lipoprotein (LDL), increase their pro-inflammatory and immunogenic potential, accelerating their cellular uptake and plaque

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progression. Moreover, oxidation impairs the atheroprotective activity of high-density lipoprotein (HDL), reducing cell cholesterol efflux and its removal from plaques. Fibroblasts migrating from the adventitia contribute to the fibrotic process and together with other resident or infiltrating cells remodel interstitium composition through the impaired balance between metalloproteases and their inhibitors. At any stage, the changes in chemical properties of the intimal surface facilitate platelet and leukocyte adhesion and eventually thrombosis. The acute swelling and rupture are typical of soft plaques, rich in free lipids and inflammatory cells, and characterized by a thin fibrous cap. Intraplaque hemorrhage or thrombosis eventually causes acute ischemic events.

In the last decades, clinical studies, animal models, and in vitro works have provided evidence that immune responses are involved in plaque formation through immune cell migration in the intima and local activation, and through autoantibodies. These immune responses may be triggered by infectious agents and/or neoantigen exposition on endothelium activated by stressors including classical atherogenic factors [1]. The primary rather than the secondary role of immunity in plaque formation is supported not only by the demonstration of activated immunocompetent T lymphocytes and dendritic cells in early lesions in young subjects but also by experiments in which defective immune responses were shown to be protective against the plaque formation. More recent evidence has suggested that the inflammasome plays a role in plaque formation as AS development is inhibited in mice knocked-out for the inflammasome-related gene NLRP3 [4].

The involvement of autoimmune responses is proven by the identification of autoantigens, the results of studies on animal models (active immunization and passive transfer), and clinical evidence. B2-Glycoprotein I (β2GPI), the main target antigen recognized by antiphospholipid antibodies, can be found in human AS specimens from carotid endarterectomies, it is abundantly expressed within the subendothelial regions and the intimal–medial border of human AS plaques, and it colocalizes with $CD4^+$ lymphocytes [1]. Immunization of mice with β2GPI resulted in a pronounced cellular response to β2GPI and high titers of anti-β2GPI antibodies associated with larger AS lesions containing abundant $CD4^+$ cells [1]. T lymphocytes from β2GPI-immunized LDL-receptor-deficient mice induce an increase in fatty streaks dimension when injected into syngenic mice, compared with control lymphocytes [1].

The evidence supporting accelerated AS as the pathogenetic mechanism underlying atherothrombotic events in patients with primary APS (as opposed to APS secondary to other rheumatic diseases, especially SLE) is controversial. Recent studies offered a possible explanation supporting the occurrence of an atherothrombotic process rather than an increased plaque burden, at least in patients with primary APS. In APS, β2GPI-specific T cells have been found in atherosclerotic plaques where β2GPI promotes a local Th1 inflammatory response potentially leading to plaque instability and rupture, eventually leading to atherothrombotic arterial involvement. Similar findings have been demonstrated in APS secondary to SLE where pro-inflammatory cytokines (IL17, IFNγ) production is induced by β2GPI in activated plaque-derived T cells infiltrating atherosclerotic lesions promoting plaque instability and subsequent possible arterial thrombosis [5].

B2GPI can form complexes with oxidized LDL (oxLD), and these complexes are suggested to be predictive markers of coronary artery disease severity [6]. IgG specific to the β2GPI/oxLDL complex have been demonstrated to be higher in primary APS and APS secondary to SLE compared to SLE without APS or to RA, especially in patients experiencing a previous thrombotic event, as a possible sign of the extent of vascular involvement. Circulating IgG anti-β2GPI/oxLDL complexes can promote the macrophage uptake of the complexes and facilitate β2GPI-epitopes presentation to pathogen autoreactive T cells. Thus, in an autoimmune background, circulating β2GPI/oxLDL can be implicated as atherogenic autoantigens and may act as risk factors and possibly contributors to thrombosis and AS [6].

As said, oxLDL is more likely to accumulate in macrophages and VSMCs compared to native LDL. Besides this intrinsic proatherogenic property, oxLDL induce the formation of anti-oxLDL antibodies that can be atheroprotective in the case of IgM, or potentially associated with increased CVR in the case of IgG [7]. Thus, also B lymphocyte activity appears to influence atherosclerotic risk and progression. Indeed, B1 CD5+ lymphocytes are a small component of the innate immune system with an atheroprotective role that might be exerted through the secretion of anti-oxLDL IgM, inhibiting oxLDL accumulation in macrophages. On the other hand, B2 lymphocyte subsets are associated with IgG secretion and progression of AS [8]. T-cells have been demonstrated to play a pivotal role in specific settings.

Heat shock proteins (HSPs) are a family of phylogenetically highly conserved stress proteins, among which human HSP60 has been recognized as an important autoantigen in AS. Anti-HSP antibodies are produced in response to both endogenously expressed HSP and microbial HSP due to cross-reactivity. Circulating levels of both HSP60, released by activated/damaged cells, and anti-HSP60 antibodies correlate with clinically evident AS and sonographically demonstrable AS lesions [1]. Recent evidence points to periodontal disease and specific infections (e.g., by Porphyromonas Gingivalis) as direct risk factors for the progression of AS. Periodontal pathogens have been found within the atherosclerotic plaque and patients with periodontitis have increased CVR [9]. Moreover, many other factors such as smoke, shear stress, hyperglycemia, oxLDL, oxygen radicals, and pro-inflammatory cytokines promote HSP exposition on endothelial cells (EC) and facilitate in situ autoantibody pro-inflammatory action. The endothelium is considered univocally in all pathogenic hypotheses as pivotal in AS plaque development given its ability to regulate vessel tone and interfere with inflammatory processes and coagulation. Indeed, EC are not only a target for immune and non-immune aggression but also active elements inducing vascular damage. Activated EC express class II major histocompatibility complex (MHC) molecules, functioning as antigen-presenting cells [1]. Thus, they might cooperate with the vascular-associated lymphoid tissue in mounting the adaptive immune responses to endogenous (oxLDL, HSP or β2GPI) or exogenous (infectious antigens) molecules involved in the early phases of the atherosclerotic process.

Immune and autoimmune reactions may be involved also in acute AS events, due to plaque rupture and thrombosis, by augmenting the quote of inflammatory infiltrate (and thus plaque instability), macrophage cholesterol uptake (in the case of anti-oxLDL IgG) and EC activation/damage with changes in surface properties (e.g., tissue factor expression and impairment of the fibrinolytic system).

While most studies have focused on inflammation in atherosclerotic lesions and intima, recent evidence suggests that inflammation might also start from the outer vascular and perivascular structures, including the adventitia and the vasa vasorum. Involvement of the vasa vasorum may cause hypoperfusion and injury of the macrovessels, leading to increased susceptibility to the formation and destabilization of atherosclerotic plaques. These infiltrates have been described to be more frequent and extensive in patients with AIRD than in the general population and might resemble mild forms of vasculitis [1, 10]. The presence and extent of aortic adventitial inflammatory cells have been correlated with the circulating levels of TNF receptor-1, von Willebrand factor, and osteoprotegerin (OPG). OPG is a member of the TNF receptor superfamily involved in bone metabolism but also related to increased CVR. OPN is increased in patients with AIRDs, including RA, and opens a novel perspective on the OPG/RANKL/RANK pathway as a therapeutic target in CV disease [1].

Prevalence

An accurate estimation of the prevalence of accelerated AS in patients with AIRD varies according to detection method, patient population, disease duration, and study design. Nevertheless, all studies are concordant in reporting an increased risk of AS and CV events in patients with AIRD compared to matched control groups, regardless of the means of assessment (e.g., carotid IMT measurement, coronary artery calcium score). Table 76.1 provides a summary of the reported prevalence/relative risk according to the type of AIRD. Patients with AIRD, particularly those with SLE, systemic sclerosis, and RA, generally have at least a twofold increased risk for AS and CV events compared to matched healthy controls.

Table 76.1 Prevalence of subclinical/accelerated atherosclerosis and risk for major cardiovascular events in systemic autoimmune rheumatic diseases

	Prevalence of subclinical atherosclerosis[a] (%)	Risk of symptomatic cardiovascular events
SLE	20–37	RR 1.98 (95% CI: 1.18–3.31)
RA	33–52	RR 1.55 (95% CI: 1.18–2.02)
SSc	28–64	RR 3.59 (95%CI: 2.81–4.59)
APS[b]	8–35	RR 3.58 (CI 1.29–9.92)[c]
Sjogren syndrome	49	RR 1.28 (95% CI: 0.11–1.46)
Primary small vessel vasculitis	58	RR 1.65 (95% CI: 1.23–2.22)

SLE systemic lupus erythematosus, *RA* rheumatoid arthritis, *SSc* systemic sclerosis, *APS* antiphospholipid syndrome

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[a] Assessed as carotid plaque prevalence or frequency of carotid intima-media thickness increase

[b] Prevalence significantly higher in SLE-APS vs. primary APS

[c] APS-related arterial thrombosis

Diagnosis

The diagnosis of atherosclerotic disease relies mostly on clinical picture (signs and laboratory parameters indicating tissue or organ ischemic damage) and on instrumental studies (sonography, computed tomography, magnetic resonance angiography, angiography). However, AS starts early in life and develops insidiously, and usually signs and symptoms show when the disease is in an advanced stage. For these reasons, and for the major epidemiologic relevance of AS in developed countries, nowadays most of the scientific efforts are aimed at finding sensitive and specific clinical conditions, laboratory parameters and instrumental data to assess and stratify AS-based CVR and to suggest prevention strategies. The diagnosis of autoimmune disease should induce careful assessment of the cardiovascular state in a single patient and is part of the international recommendations for all AIRDs. In general, the risk assessment for each individual relies on score risk charts that take into account the weight of association of risk factors such as age, cholesterolemia, blood pressure and smoking [11]. However, due to the complexity of the mechanisms underlying AS in AIRDs, traditional scores predicting CVR are often insufficient and underestimate the risk in these patients. Thus, specific approaches are recommended in terms of both CVR prediction and AS assessment.

Biomarkers

Lipid levels and function in patients with AIRDs need to be specifically evaluated considering the phase of disease activity and ongoing pharmacologic treatment. In fact, on one side, systemic inflammation is associated with lipid catabolism and reduction of total and LDL cholesterolemia. As a consequence, for example, very low LDL levels may be associated with increased CVR in active RA, the so-called lipid paradox. Moreover, systemic inflammation is also responsible for altered LDL and HDL functions, with increased serum cholesterol loading capacity (CLC) and reduced cell cholesterol efflux capacity (CEC) , respectively, detected in various AIRDs [12, 13]. Recent reports showed that such lipoprotein function derangements are associated with increased AS and CVR in RA [13]. CLC and CEC measurement is not yet available in clinical practice, but these data suggest that simple classical serum lipid profile should be interpreted critically in AIRDs.

On the other side, anti-rheumatic drugs often increase serum lipid levels, but at the same time their use associates with reduced CVR, by blocking inflammation and restoring lipoprotein normal functions (see below).

Other biomarkers of CVR in AIRDs are those reflecting the systemic inflammatory state. C reactive protein (CRP), produced mainly by hepatocytes and endothelial cells, is a pentameric protein of the pentraxin superfamily that contributes to inflammation, oxidative stress, and endothelial activation. Its serum levels increase slightly in low grade inflammation and massively in acute conditions such as infections and AIRDs flares. Circulating CRP is a strong CVR marker: levels below 1 mg/L are considered low risk, levels between 1 and 3 mg/L are considered moderate risk, and levels exceeding 3 mg/L are considered high risk [14]. Homocysteine is a pro-inflammatory and pro-oxidant molecule and its serum level increase is a marker of AS in selected populations, including patients with RA [15].

Other potentially interesting parameters, such as circulating cytokines, NET products, non-coding RNAs at present seem to be not clinically useful for various reasons: they might not reflect local arterial concentration, inflammation, and lesion type or extension; they might be part of a complex network, with little significance as single parameters; they do not associate clearly with CV events [16, 17].

Finally, specific disease-associated parameters may be useful for CVR assessment. For example, in RA, seropositivity for rheumatoid factor and anti-citrullinated peptide antibodies is associated with increased CVR [11].

Instrumental Tools

AS assessment can be performed through the well-established use of ankle–brachial index, which reflects peripheral artery disease, of pulse wave velocity, a measure of arterial stiffness, and of the carotid intima-media thickness (IMT) measurement by ultrasound [18]. Carotid IMT and arterial stiffness are early signs of subclinical AS that precede the appearance of established plaques. Arterial stiffness measured with pulse wave velocity in large arteries has been proposed as a valid surrogate marker of AS and has been studied in patients with AIRDs [18].

Coronary artery calcium score, obtained by tomographic evaluation, is a highly specific feature of coronary AS and has emerged as a widely available, reliable means of evaluating the risk for major CV events. CT angiography plaque burden assessment is another tool that has become part of the CVR assessment of patients at increased risk of major CV events. Furthermore, non-invasive methods to evaluate endothelial function are available, such as reduced flow-mediated vasodilation, or are being developed, such as coronary MRI combined with an endothelial stressor (e.g., isometric handgrip exercise). Positron emission tomography (PET) with specific tracers has been tested to evaluate myocardial blood flow and endothelial function. Nevertheless, the standardization and widespread applicability of these endothelial evaluating tests is still a matter of debate [17, 18].

The future direction of research in the field of early diagnosis and potential treatment of accelerated AS includes the application of nanotechnology-assisted biosensing to improve the detection of biomarkers and nanotechnology-assisted molecular imaging for the very early diagnosis of CV involvement. Moreover, artificial intelligence-based preventive, precision, and personalized models to accurately predict the individual CV risk in patients with AIRD are being explored.

Therapy

Current principles for the prevention and therapy of AS are largely described in the literature. Interventions on lifestyle, diet, body weight, and pharmacologic treatment in AIRDs are generally the same as those recommended for the general population [19].

However, some additional principles can be applied, on the basis of the specific pathogenic mechanisms of AS in the context of autoimmune diseases.

First of all, more aggressive goals for risk factor reduction in AIRD have been suggested. Second, lipid management should be individualized in patients with AIRD, taking into account disease activity, disease severity and medications. In particular, the use of statins in AIRDs may be beneficial because they not only regulate serum cholesterol levels, but also have anti-inflammatory and immunomodulatory effects and reduce disease activity [19].

Third, the control of inflammation and disease activity is a pivotal aspect of preventing AS progression. Among the available anti-rheumatic agents, the greatest anti-atherogenic activity has been demonstrated for DMARDs, particularly for biologic DMARDs [2, 3], through their multiple effects on plaque formation, arterial stiffness, endothelial function, lipoprotein function, and insulin resistance. In specific cases, there are conflicting results on the relationship between CV disease and anti-rheumatic drugs. One of these involves JAK-path inhibition, as tofacitinib use has been associated with a possible increased risk of major adverse cardiovascular events (MACE) in patients over 60 with at least one CV risk factor. According to the currently available data, it seems that tofacitinib might promote CV events favoring thrombosis rather than inducing AS progression [20].

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Idiopathic Interstitial Pneumonias

77

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Abstract

Idiopathic interstitial pneumonias are a group of diffuse parenchymal lung diseases of unknown etiology with varying degrees of inflammation and fibrosis. They are classified into eight clinicopathological entities: idiopathic pulmonary fibrosis, nonspecific interstitial pneumonias, desquamative interstitial pneumonias, respiratory bronchiolitis–associated interstitial lung diseases, organizing pneumonias, acute interstitial pneumonias, lymphoid interstitial pneumonias, and pleuroparenchymal fibroelastosis. The diagnosis of idiopathic interstitial pneumonias is typically made through a clinical-radiological-pathological approach and requires an assessment from a multidisciplinary committee. For idiopathic pulmonary fibrosis, a defined set of radiological criteria has been established, enabling diagnosis with a sensitivity exceeding 90%. Bronchoscopic lung cryobiopsy has a high diagnostic yield and can be an alternative to lung biopsy in centers with experience in the area. The multidisciplinary committee is currently considered the gold standard in the area of interstitial lung diseases and therefore of idiopathic interstitial pneumonias. Currently, there are two anti-fibrotic treatments, nintedanib and pirfenidone, and a lung transplant might be necessary in the advanced stages.

Keywords

Idiopathic interstitial pneumonias · Interstitial lung disease · Idiopathic pulmonary fibrosis · Bronchoscopic lung cryobiopsy · Multidisciplinary committee

Classification of Idiopathic Interstitial Pneumonias

The idiopathic interstitial pneumonias (IIPs) are a group of diffuse parenchymal lung diseases of unknown etiology with varying degrees of inflammation (alveolitis) and fibrosis [1]. The histopathological classification of the IIPs has evolved over time. Evidence that accumulated over the next decade led to guidelines that further refined the definition of IIPs and established novel criteria for the radiological and histopathological features in the American Thoracic Society (ATS)/European Respiratory Society (ERS) 2013 consensus classification statement [2]. This classification separates the IIPs into eight clinicopathological entities (Table 77.1), which in turn can be divided into three groups: major (with acute, subacute, or chronic clinical course), rare, and unclassifiable. Within the group of chronic fibrosing interstitial pneumonias, idiopathic pulmonary fibrosis (IPF) is characterized by the presence of usual interstitial pneumonia (UIP) in the histological examination of lung parenchyma. The UIP pattern should not be equated with the diagnosis of IPF, as this histological pattern can also be associated with connective tissue diseases (CTDs), drug-induced interstitial pulmonary disease, chronic hypersensitivity pneumonitis (HP), pleuroparenchymal fibroelastosis (PPFE), pneumoconiosis, and familial pulmonary fibrosis (FPF). Over the last decade, there has been increased clarity in defining the clinical, radiological, and pathological characteristics that have facilitated the differentiation of these entities from idiopathic interstitial pneumonias (IIPs), especially idiopathic pulmonary fibrosis (IPF) and idiopathic nonspecific interstitial pneumonia (NSIP) [2]. NSIP includes the presence of a uniform interstitial cellular infiltrate with lymphoplasmacytic infiltration of the alveolar septa distributed uniformly. This contrasts with the UIP pattern, which presents a heterogeneous distribution. NSIP manifests in two histopathologic forms: cellular and fibrotic patterns and has been identified as an entity that can evolve into fibrosis. NSIP may occur without a known cause (idiopathic) or be linked to CTD,

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Table 77.1 Classification and categorization of idiopathic interstitial pneumonias

	Category	Clinical diagnosis	Pathological pattern
Major idiopathic interstitial pneumonia	Chronic fibrosing IIP	Idiopathic pulmonary fibrosis (IPF)	Usual interstitial pneumonia (UIP)
		Nonspecific interstitial pneumonia (NSIP)	NSIP cellular
			NSIP fibrotic
	Respiratory bronchiolitis–associated interstitial lung disease (RB-ILD)	RB-ILD	RB-ILD
		Desquamative interstitial pneumonia (DIP)	DIP
	Acute/subacute IIP	Acute interstitial pneumonia (AIP)	Diffuse alveolar damage (DAD)
		Organizing pneumonia (OP)	OP
Rare idiopathic interstitial pneumonia		Lymphoid interstitial pneumonia (LIP)	LIP
		Idiopathic pleuroparenchymal fibroelastosis (PPFE)	PPFE
Unclassifiable idiopathic interstitial pneumonia			Overlap of histologic patterns

IIP idiopathic interstitial pneumonia, *IPF* idiopathic pulmonary fibrosis, *UIP* usual interstitial pneumonia, *NSIP* nonspecific interstitial pneumonia, *RB-ILD* respiratory bronchiolitis–associated interstitial lung disease, *DIP* desquamative interstitial pneumonia, *AIP* acute interstitial pneumonia, *DAD* diffuse alveolar damage, *OP* organizing pneumonia, *LIP* lymphoid interstitial pneumonia, *PPFE* idiopathic pleuroparenchymal fibroelastosis

Adapted from American Thoracic Society/European Respiratory Society [1] and Travis et al. [2]

drug-induced interstitial pulmonary disease, hypersensitivity pneumonitis, and, in some cases, FPF. Multidisciplinary discussion (MDD) is crucial in differentiating NSIP from other interstitial lung diseases (ILDs). Within the group of smoking-related interstitial pneumonias, we can find the respiratory bronchiolitis–associated interstitial lung disease (RBILD) and the desquamative interstitial pneumonia (DIP). Both entities encompass a histologic continuum characterized by macrophage accumulation. The differentiation between these entities relies on the extent and distribution of this process, along with the corresponding pattern evident in HRCT. Despite sharing histological similarities, they exhibit distinctions in clinical presentation, imaging characteristics, and responses to therapy, thus warranting their separate classification. Cryptogenic organizing pneumonia (COP) remains included in the classification of IIP due to its idiopathic origin and the occasional propensity to be mistaken for other forms of IIP, especially when there is progression to fibrosis. However, organizing pneumonia (OP) can also be associated with CTD, drug-induced interstitial pulmonary disease, radiotherapy, inhalation of toxic substances, pulmonary infections, or inflammatory bowel diseases. It is likely that certain patients reported with fibrotic NSIP belong to the subgroup characterized by a fibrosing variant of OP. Among patients displaying this mixed fibrosis and OP pattern, some are discovered to have underlying conditions such as polymyositis or antisynthetase syndrome. Therefore, a thorough follow-up and careful MDD evaluation are crucial in these patients. The term acute interstitial pneumonia (AIP) is used exclusively for cases of idiopathic acute respiratory distress syndrome. Within the group of rare IIP, we can find the lymphoid interstitial pneumonia (LIP) and the PPFE. LIP is usually associated with other disorders, such as CTDs (Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus), autoimmune diseases (Hashimoto's disease, myasthenia gravis, pernicious anemia, primary biliary cholangitis), immunodeficiencies (agammaglobulinemia), and human immunodeficiency virus (HIV), even though idiopathic cases still occur infrequently. Idiopathic pleuroparenchymal fibroelastosis is a rare IIP characterized by elastotic fibrosis that covers the pleural and subpleural regions of the lung parenchyma, with predominance on the upper lobes [2, 3]. About half of the patients have a history of recurrent infections, and a minority present with familial interstitial lung disease and nonspecific autoantibodies, although the idiopathic nature is observed in several cases.

Unclassifiable idiopathic interstitial pneumonia occurs when the final diagnosis may not be achieved, even after extensive multidisciplinary evaluation. This occurs in the setting of discordance between clinical, radiological, or pathological findings [2]. On the other hand, a significant proportion of patients with IIP exhibit autoimmune features, but do not fulfill the diagnostic criteria for a definite CTD. As a result, the term interstitial pneumonia with autoimmune features (IPAF) was introduced in 2015 to define the combination of an ILD with clinical, serological, and morphological criteria that derive from an underlying autoimmune disease suggestive of, but not definitive for, a CTD [4]. These classification criteria were established by integrating features from three domains: a clinical domain consisting of extra-thoracic features, a serologic domain with specific autoantibodies, and a morphologic domain with imaging patterns, histopathological findings, or multi-compartment involvement. The management should be meticulously tailored on a case-by-case basis, given the extensive heterogeneity observed in these patients. As recognized by the ATS/ERS "Task Force on undifferentiated Forms of connective tissue disease–associated interstitial lung disease," the suggested classification scheme for interstitial pneumonia with autoimmune features (IPAF) is a research concept that will require further revision and refinement based on data to enhance prognostic insights and optimize patient care.

Clinical Manifestations

The most common symptoms are dyspnea on exertion and dry coughing. Dyspnea typically begins gradually but progresses over time. The onset of the disease may be insidious, subacute, or abrupt, depending on the type of IIP, with an age range and preference in gender. Some clinical entities can cause constitutional symptoms. The most useful information obtained from the physical examination is the presence of crackles and finger clubbing, although these signs are more prevalent in chronic fibrosing interstitial pneumonias such as IPF and NSIP [1, 3, 5–11]. Table 77.2 provides a summary of the key clinical features.

Diagnostic Approach

Biomarkers

The identification of biomarkers has primarily centered on IPF, typically in small cohorts without independent validation. Nonetheless, there are some emerging findings that could hold implications for the diagnosis, management, or prognostication of other IIPs. In an appropriate clinical context, those tests can support a specific diagnosis. The panel must include a complete hemogram that measures the erythrocyte sedimentation rate (ESR), the level of C-reactive protein (CRP), the level of serological electrolyte concentration that includes calcium, urea, creatinine, liver function, and urinary sediment tests. To better evaluate an associated CTD, it is also recommended to perform antibody (Ab) serology tests that include antinuclear Ab (ANA), extractable nuclear antigens (ENA), rheumatoid factor (FR), cyclic citrullinated peptide (CCP) Ab, antiJo-1 Ab, creatine kinase (CK), and aldolase (Table 77.3). However, there is no consensus on the most appropriate antibody panel for the initial examination of an ILD, and its sensitivity and specificity remain unknown. In addition, it has been documented that 10–20% of the patients that suffer from IPF have a positive result on an ANA or RF test, although titers are low [13].

Regarding biomarkers for differential diagnosis, some of them seem to distinguish patients with IPF from non-IPF patients, including cytokines such as Krebs Von der Lungen 6 (KL-6) as an indicator of alveolar damage associated to acute exacerbation of IPF and acceleration of the disease, and CCL-18; metalloproteinases (MMP), mainly MMP-7

Table 77.2 Frequency and clinical characteristics of idiopathic interstitial pneumonia

	IPF	NSIP	RB-ILD	DIP	AIP	OP	PPFE	LIP
Frequency	~47–64	~14–36	10–17%		<2%	4–12%	5–8%	<2%
Onset	Insidious	Insidious/ subacute	Insidious/subacute		Abrupt (1–2 weeks)	Subacute	Insidious/subacute	Insidious/subacute
Gender (M/F)	M	F	M = F	M > F	M = F	M = F	M = F	F > M
Age	~60	~50	~44 (40–50)		~57	~50–60 (17–95)	~49 (13–85)	~50 (40–50)
Finger clubbing	~50%	10–30%	<10%		No	<3%	No	No
Crackles	90%	79–100%	50%		No	60%	No	No
Constitutional symptoms	No	Depends on etiology	No		Fever arthralgias asthenia weight loss	Fever weight loss	Weight loss, pleuritic pain if pneumothorax	Fever arthralgias asthenia weight loss night sweats

IPF idiopathic pulmonary fibrosis, *NSIP* nonspecific interstitial pneumonia, *RB-ILD* respiratory bronchiolitis–associated interstitial lung diseases, *DIP* desquamative interstitial pneumonia, *AIP* acute interstitial pneumonia, *OP* organizing pneumonia, *PPFE* idiopathic pleuroparenchymal fibroelastosis, *LIP* lymphoid interstitial pneumonia

Adapted from Shoenfeid et al. [12]

Table 77.3 Proposed list of peripheral blood and antibody tests

Complete blood count (CBC)
Erythrocyte sedimentation rate (ESR)
C reactive protein (CRP)
Levels of Ca^{+}
Blood urea nitrogen (BUN)
Creatinine
Liver function tests (LFT)
Urinary sediment
ANA high titles are suggestive of CTD
ANCA (MPO and PR3)
Rheumatoid factor (RF): in RA and others CTD
Anti-cyclic CCP: associated with RA
Anti-Scl-70: associated with SS
Anti-RNP (anti-ribonucleoprotein): associated with CTD
Anti-Jo-1: associated with myositis
Anti-Ro (SS-A), anti-La (SS-B): associated with SSj
CPK/aldolase: increased in myositis
Panel of myositis: – Antisynthetase antibodies: PL7, PL12, EJ, and OJ – MDA-5: associated with Gottron papules and aggressive ILD – PMScI: PM and SS overlap – Ro-52: associated with more aggressive ILD. Also associated with SSj

ANA antinuclear antibody, *ANCA* cytoplasmic antineutrophil cytoplasmic antibody, *RF* rheumatoid factor, *RA* rheumatoid arthritis, *CCP* anti-cyclic citrullinated peptide, *CPK* creatine phosphokinase, *CTD* connective tissue disease, *ILD* interstitial lung disease, *SS* systemic sclerosis, *PM* polymyositis, *SSj* Sjögren's syndrome

and MMP-1; and surfactant products SP-A and SP-D, all with sensitivity and specificity around 50–60% [14]. The most important genetic markers are variants that encode proteins that synthesize or regulate the telomerase enzyme (TERT and RTEL1) and the genetic mutation that encodes MUC5B. The common variant of the MUC5B gene, rare TERT and RTEL1 telomerase variants, and telomere shortening are also associated with a greater risk of developing an IPF and familial interstitial pneumonias (FIP) [15]. In spite of the usefulness that biomarkers have demonstrated, the guidelines still do not recommend their use due to the low quality of the evidence provided during clinical trials, although scientific advances are moving toward its global validation.

Radiology

Chest X-ray findings in patients with IIP consist of interstitial patterns that affect both hemithoraces diffusely. At the time of diagnosis, the chest X-ray may be normal in 10% of the cases. High-resolution computed tomography (HRCT) is a more sensitive tool than chest X-ray in the evaluation of abnormalities of the pulmonary interstitium and has become indispensable for diagnostic approach. The major findings are ground glass opacities, consolidation, linear and reticular opacities, centrilobular nodules, traction bronchiectasis, and honeycombing. Their distribution is different in each disease, and this narrows the differential diagnosis (Table 77.4). In IPF, four HRCT categories were defined in the 2018 guidelines for diagnosis of IPF: UIP pattern, probable UIP pattern, indeterminate for UIP pattern, and alternative diagnosis. HRCT findings of a UIP pattern is a characteristic feature, but it can also be observed in individuals with other ILD. The HP-UIP and CTD-UIP cases may be suspected based on imaging characteristics but are frequently radiologically indistinguishable from IPF-UIP. In a proper context, when it comes to a radiologic diagnosis of a UIP in a pathologic diagnosis of a UIP, they have a positive predictive value (PPV) of around 90–100%. The probable UIP pattern has provisional high confidence (70–89%), and indeterminate for UIP has provisional low confidence (51–69%) [14, 16].

Lung Function Testing

Patients with suspected IIP should undergo lung function tests. While they may not indicate a specific diagnosis, these assessments are essential for evaluating respiratory limitations and for ongoing follow-up [13]. The arterial blood gas test and the 6-min walking test both measure hypoxemia and desaturation, both at rest and during exertion. Forced spirometry with a non-obstructive pattern, decreased lung volumes that mostly result in a restrictive ventilatory pattern (decrease in total lung capacity (TLC) and forced vital capacity (FVC) and the DLco (diffusing capacity of the lungs for carbon monoxide) test, shows a reduced diffusing capacity.

Bronchoscopy

A bronchoscopy can be performed on patients who suffer an IIP to obtain material for microbiological, cytological, and histological analysis. The different procedures used are bronchoalveolar lavage (BAL), transbronchial lung biopsy (TBLB), and transbronchial lung cryobiopsy (TBLC). In most cases, a BAL is employed to assist in diagnosis, either by substantiating a provisional diagnosis or indicating an alternative. In IPF, a BAL cell count has only a limited role in diagnosis and does not clearly differentiate between IPF and fibrotic NSIP, either diagnostically or prognostically [17]. However, BAL in IPF should be considered in all patients with suspected infection, malignancy, or acute exacerbations. In some cases of IPF, it shows increased neutrophils and eosinophils. In patients with increased lymphocytes, other alternative diagnoses should be excluded, like OP or NSIP. In OP patients, a BAL reveals marked lymphocytosis,

Table 77.4 High-resolution computed tomography (HRCT) findings in idiopathic interstitial pneumonias

Probable disease	Scanning patterns	Main HRCT findings	Distribution
IPF	UIP	Honeycombing with or without traction bronchiectasis Presence of irregular thickening of interlobular septa Usually superimposed with a reticular pattern, mild ground glass opacities (GGO) May have pulmonary ossification	Subpleural basal predominant often heterogeneous (areas of normal lung interspersed with fibrosis) may be asymmetric
	Probable UIP	Reticular pattern with traction bronchiectasis/bronchiolectasis May have mild GGO Absence of subpleural sparing	Subpleural and basal predominant Heterogeneous (areas of normal lung interspersed with reticulation and traction bronchiectasis/bronchiolectasis)
	Indeterminate for UIP	Subtle reticulation. May have mild GGO or distortion	Subpleural and basal predominant
	Alternative diagnosis	Cysts Marked mosaic attenuation Predominant GGO Profuse micronodules Centrilobular nodules Nodules Consolidation	Peribronchovascular Perilymphatic Upper or mid-lung
NSIP	NSIP	GGO Reticular opacities Consolidation Traction bronchiectasis	Peripheral Subpleural Basal
RB-ILD	RB-ILD	Bronchial wall thickening Centrilobular nodules GGO	Multifocal Diffuse
DIP	DIP	GGO Reticular opacities	Multifocal Peripheral
AIP	AIP	Consolidation GGO	Diffuse
OP	OP	Consolidation GGO	Subpleural Peribronchiolar
LIP		GGO Thin-walled cysts Centrilobular nodules Linear opacities	Diffuse Lower zone bilateral
FEEP		Irregular pleural thickening Dense reticular fibrosis	Diffuse pleural Upper Lober Bilateral

GGO ground-glass opacity, *IPF* idiopathic pulmonary fibrosis, *NSIP* nonspecific interstitial pneumonia, *RB-ILD* respiratory bronchiolitis–associated interstitial lung disease, *DIP* desquamative interstitial pneumonia, *AIP* acute interstitial pneumonia, *OP* organizing pneumonia, *LIP* lymphoid interstitial pneumonia, *PPFE* idiopathic pleuroparenchymal fibroelastosis

Adapted from American Thoracic Society/European Respiratory Society [1], Travis et al. [2] and Raghu et al. [14]

often associated with moderate neutrophilia and/or eosinophilia, together with a decreased CD4þ/CD8þ T-lymphocyte ratio. Smoking-related IIPs are characterized by the presence of numerous pigmented macrophages. A single-cell analysis of a BAL is insufficient to diagnose an IIP; nevertheless, in some appropriate clinical and radiological contexts, this can support a specific diagnosis [18]. The diagnostic yield of TBLB is 34.1%, but this procedure is not recommended with an IPF in a radiological context of a UIP [14, 16]. In recent years, the scientific evidence of its performance for undetermined ILDs has increased and can be seen as an alternative to lung biopsy in centers with experience in the area, with a yield of around 77–85% depending on the number of samples obtained [19]. The estimated yield of TBCB is 80%, and this technique may be preferred to surgical lung biopsy (SLB) in centers with appropriate expertise and/or in some patient populations.

Lung Biopsy

It is currently done through video-assisted thoracoscopic surgery (VATS) with patients appropriately selected and has an estimated yield of 90%. A subsequent SLB may be justified in some patients with nondiagnostic findings on TBLC.

Genomic classifier testing predicts histopathologic UIP in patients with ILD with a specificity of 92%, and sensitivity is only 68%; however, additional studies are necessary to obtain more precise estimates of sensitivity and specificity [19].

Multidisciplinary Approach

The diagnosis of IIPs involves a dynamic integrated approach using MDD. The diagnostic strategy starts with a systematic initial assessment [20]. The acute, subacute, and/or chronic clinical course along with the context of the disease at the time of diagnosis should encompass the presence of pulmonary and/or systemic manifestations of the disease. Figure 77.1 shows a diagnostic algorithm for IIPs, with HRCT recognized as a pivotal and initial diagnostic test. The MDD, acknowledged as the gold standard in the diagnosis of ILD, comprises a team of specialists, including pulmonologists, radiologists, autoimmune disease experts, and anatomopathologists, among others [14, 19]. This team may employ various diagnostic tools to conduct additional diagnostic steps, with the aim of establishing a precise diagnosis. Additionally, it is crucial to stratify the behavior of the IIP. Currently, in clinical practice, the definition of progressive pulmonary fibrosis (PPF) has been given as an evolutionary clinical characteristic, not as a diagnosis itself, with a highprognostic value that can direct a possible treatment. In patients with ILD that occurred with or without a known cause, PPF is defined when at least two of the following three criteriaoccured since the previous year, with no alternative explanation: worsening respiratory symptoms, physiological evidence of such worsening with absolute decrease ≥5% of the FVCor absolute decrease ≥10% of Dlco, and radiological progression of the disease. [19].

Treatment Options

The fundamental aims of the current therapy are to halt the progression of the disease and mitigate the onset of complications. In 2015, a significant milestone in the treatment of IPF, the most prevalent among IIP, was achieved. During this year, the recommendation of two anti-fibrotic drugs, nintedanib and pirfenidone, marked a pivotal development for the

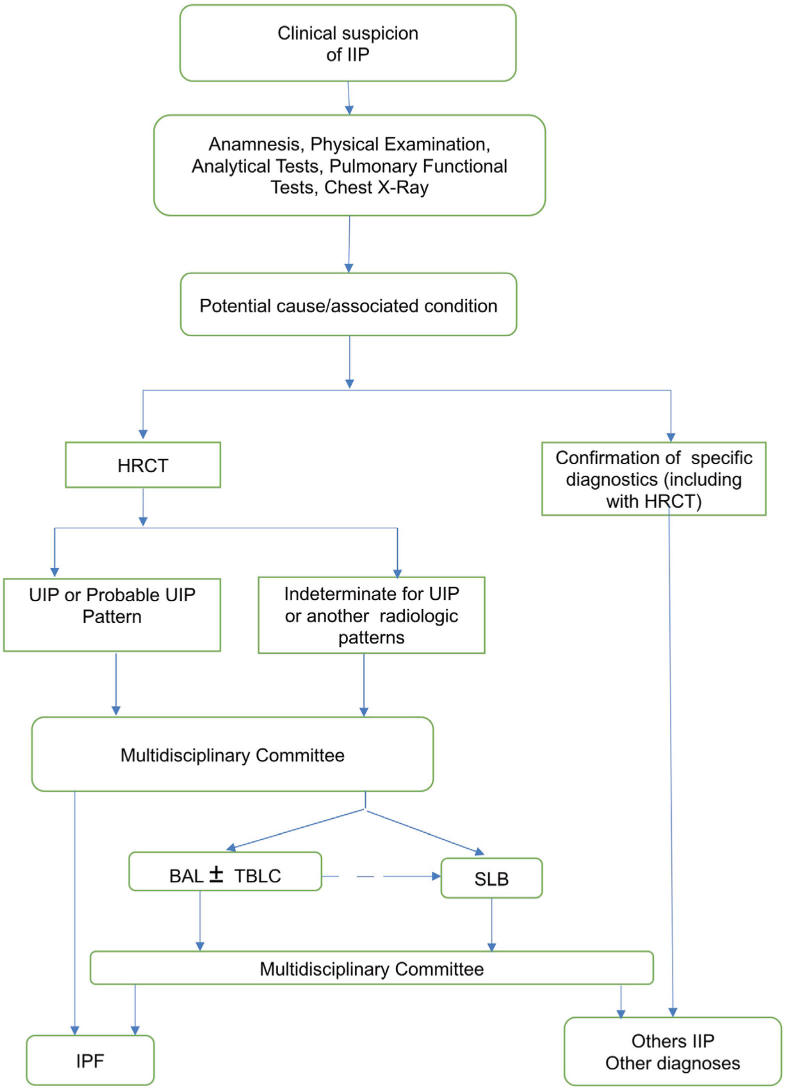
Clinical suspicion of IIP
Anamnesis, Physical Examination, Analytical Tests, Pulmonary Functional Tests, Chest X-Ray
Potential cause/associated condition
HRCT
Confirmation of specific diagnostics (including with HRCT)
UIP or Probable UIP Pattern
Indeterminate for UIP or another radiologic patterns
Multidisciplinary Committee
BAL ± TBLC
SLB
Multidisciplinary Committee
IPF
Others IIP Other diagnoses

Fig. 77.1 Diagnostic algorithm for idiopathic interstitial pneumonia (IIP). *BAL* bronchoalveolar lavage fluid, *TBLC* transbronchial lung cryobiopsy, *Usual Interstitial SLB* surgical lung biopsy, *HRCT* high-resolution computed tomography. (Adapted from Raghu et al. [19])

disease with a typically grim prognosis at 5 years. Building on these advancements, in 2022, the recommendation for anti-fibrotic treatment was extended to ILD exhibiting criteria of PPF [19]. Glucocorticoids are usually used as initial treatment in monotherapy in COP, AIP, and LIP. In RBILD and DIP with the suppression of tobacco consumption and the administration of glucocorticoids, an improvement of the disease was observed in some series. The recommended treatment for NSIP consists of the administration of glucocorticoids in association or in combination with immunosuppressant agents. Fibrotic patterns (UIP and fibrosing NSIP) are used in exacerbations or clinical worsening of unclear causes. Cytotoxic immunosuppressive drugs that are commonly used to tread CTD-associated IIP include azathioprine, mycophenolate, cyclophosphamide, calcineurin inhibitors (in inflammatory myopathies), and leflunomide. In case of progression, despite initial treatment with glucocorticoids and immunosuppressants, there are several options like therapy with biologic drugs (rituximab, tocilizumab, or abatacept) [6, 7, 9, 10].

IIPs are associated with several comorbidities such as gastroesophageal reflux, obstructive sleep apnea, pulmonary hypertension, lung cancer, and combined pulmonary fibrosis and emphysema. Complications can result in disease exacerbation and pulmonary thromboembolism. In the event of clinical worsening, evaluating comorbidities and monitoring the emergence of complications are crucial as they can significantly impact survival outcomes. Lung transplantation emerges as the therapeutic option for conditions that progress over time, culminating in respiratory failure that proves refractory to conventional medical interventions [19, 21].

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Pulmonary Arterial Hypertension

78

Isabel Blanco and Joan Albert Barberà

Abstract

Pulmonary arterial hypertension (PAH) is the most characteristic group of pulmonary hypertensive states. Among other conditions, PAH includes the idiopathic type and forms associated with connective tissue diseases (CTDs), particularly systemic sclerosis, CREST syndrome, and mixed connective tissue disease. Symptoms and signs of PAH include shortness of breath, fatigue, syncope, chest pain, and swollen ankles. Pulmonary hypertension can be detected by transthoracic Doppler echocardiography. This procedure should be performed routinely once a year in patients with CTD with a high risk of developing PAH. The diagnosis of pulmonary hypertension needs to be confirmed by right heart catheterization. Pharmacological treatment is based on drugs that modulate endothelial function.

Keywords

Pulmonary hypertension · Pulmonary circulation · Endothelium · Echocardiography · Right heart catheterization · Prostacyclin · Endothelin-1 antagonists · Phosphodiesterase-5 inhibitors

Pulmonary Hypertension

Concept

Pulmonary circulation is a low-resistance, highly distensible system that accommodates the entire cardiac output with intravascular pressures much lower than those of the systemic circulation. The upper limit of normal resting mean pulmonary arterial pressure (PAP) is 20 mmHg. PAP varies with cardiac output, although, due to recruitment and distensibility of pulmonary vessels, it usually does not exceed 30 mmHg, even in situations of elevated cardiac output, such as during exercise.

Pulmonary hypertension (PH) is present when the mean PAP is greater than 20 mmHg, at rest. It is of precapillary origin when pulmonary vascular resistance (PVR) exceeds 2 mmHg/L/min or Wood units and of post-capillary origin when the pulmonary occlusion or wedge pressure is greater than 15 mmHg [1]. The most clinically significant consequence of PH is the overload of the right ventricle (RV), which can eventually lead to failure and result in death.

Nomenclature and Classification

PH is a hemodynamic disorder defined by an increased PAP that can be present in various clinical scenarios. The classification of processes that can lead to PH is shown in Table 78.1. Five major categories are distinguished: (1) pulmonary arterial hypertension (PAH), (2) PH associated with left heart disease, (3) PH associated with lung disease and/or hypoxia, (4) chronic thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstructions, and (5) PH of uncertain and/or multifactorial origin.

Pulmonary Arterial Hypertension (PAH)

PAH is a clinical condition characterized by precapillary PH in the absence of other causes (lung disease, pulmonary thromboembolism, or other rare diseases). It encompasses various clinical forms that share a similar clinical presentation and virtually identical anatomopathological changes in pulmonary microcirculation. Different forms of PAH are included within this category, such as idiopathic, heritable, and drug- or toxin-induced, associated with other processes, and forms that

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Table 78.1 Clinical classification of pulmonary hypertension

1. Group 1—Pulmonary arterial hypertension (PAH):
1.1. Idiopathic
1.1.1. Non-responders at vasoreactivity testing
1.1.2. Acute responders at vasoreactivity testing
1.2. Heritable
1.3. Associated with drugs and toxins
1.4. Associated with:
1.4.1. Connective tissue disease
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart disease
1.4.5. Schistosomiasis
1.5. PAH with features of venous/capillary (PVOD-PCH) involvement
1.6. Persistent pulmonary hypertension of the newborn
2. Group 2—Pulmonary hypertension associated with left heart disease
2.1. Heart failure:
2.1.1. With preserved ejection fraction
2.1.2. With reduced or mildly reduced ejection fraction
2.2. Valvular heart disease
2.3. Congenital/acquired cardiovascular conditions leading to post-capillary PH
3. Group 3—Pulmonary hypertension associated with lung disease and/or hypoxia
3.1. Obstructive lung disease or emphysema
3.2. Restrictive lung disease
3.3. Lung disease with mixed restrictive/obstructive pattern
3.4. Hypoxia without lung disease (e.g., high altitude)
3.5. Developmental lung disorders
4. Group 4—PH associated with pulmonary artery obstructions
4.1. Chronic thromboembolic pulmonary hypertension
4.2. Other pulmonary artery obstructions
5. Group 5—Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1. Hematological disorders
5.2. Systemic disorders
5.3. Metabolic disorders
5.4. Chronic renal failure with/without hemodialysis
5.5. Pulmonary tumor thrombotic microangiopathy
5.6. Fibrosing mediastinitis

involve venous or capillary disorders (pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis) (Table 78.1). The pathophysiology, pathological findings, clinical characteristics, diagnostic methods, and treatment are common to most forms of PAH.

Pulmonary Arterial Hypertension Associated with Systemic Autoimmune Disease

Pulmonary arterial hypertension is a frequent complication of systemic autoimmune diseases. The disease most frequently associated with PAH is systemic sclerosis (SSc), especially in the limited scleroderma form, which can be observed in up to 30% of patients. Changes compatible with PAH have been observed in 50% of patients with CREST syndrome. In mixed connective tissue disease, the incidence of PAH is similar to SSc, while it is lower in systemic lupus erythematosus (SLE) (5–10%). PAH is rarely associated with dermatomyositis or Sjögren's syndrome. The relationship between rheumatoid arthritis and PAH has not been clearly established.

In patients with SSc, PAH may occur isolated or in association with interstitial lung disease. Occasionally, patients with SSc may show features of venous/capillary involvement. Not rarely, myocardial involvement by SSc may produce post-capillary PH (group 2 PH). Patients with antiphospholipid syndrome may present CTEPH (group 4 PH).

Clinical Presentation

Medical History

The most common symptoms of PAH include exertional dyspnea, syncopal, or presyncopal episodes usually with exertion, chest pain, fatigue, palpitations, and peripheral edema. Due to the nonspecificity of these symptoms and their gradual onset, the diagnosis of PAH is often delayed. Syncope and chest pain with exercise suggest a greater limitation of cardiac output. It is essential to inquire about risk factors associated with pulmonary hypertension, as well as family history and the use of drugs, especially anorectics (Table 78.1) [2]. The extent to which the disease limits activities of daily living should be defined. The modified New York Heart Association (NYHA) Functional Class Scale (World Health Organization [WHO] Functional Class Scale) is used for this purpose, and it has prognostic and therapeutic utility.

Physical Examination

The most common physical signs include accentuated and/or splitting of the second heart sound at the pulmonary focus, palpable thrill on the left sternal border, systolic tricuspid regurgitation murmur, and diastolic pulmonary regurgitation murmur audible at the left sternal border (Graham-Steel murmur). When there is right ventricular dysfunction, increased jugular venous pressure, elevated "v" wave in jugular pulse, jugular engorgement, hepatojugular reflux, ankle edema, hepatomegaly, and occasionally ascites can be observed. During the physical examination, attention should be paid to signs that suggest the presence of a potentially associated systemic disease with PAH.

Diagnosis

The diagnostic process of PH consists of several phases, ranging from clinical suspicion to severity assessment (Table 78.2). The key tool for detecting PH is transthoracic

Table 78.2 Diagnosis of pulmonary hypertension

Suspicion	Symptoms, physical examination, ECG, chest X-ray
Screening	Transthoracic echocardiogram (TTE)
Classification and identification of the PH group and subgroup	• TTE (valvulopathy or left heart disease, congenital heart disease) • TTE with agitated saline (intra- or extracardiac shunting) • Respiratory function testing: forced spirometry, static lung volumes, diffusion capacity for carbon monoxide (DLCO), and arterial blood gas analysis • Pulmonary ventilation and perfusion scintigraphy • General laboratory tests and determination of: – Thyroid function – Liver function – Autoimmunity screening: anti-nuclear antibodies (ANA), anti-DNA, anti-centromere, anti-cardiolipin, and anti-U1-RNP – Serology for HIV and hepatitis B and C viruses • Optional – High-resolution chest CT scan – Helical chest CT angiography – Abdominal ultrasound – Sleep study – Selective pulmonary arteriography if CTEPH – Transoesophageal echocardiogram
Diagnosis and severity assessment	• Hemodynamic diagnosis: – Right heart catheterization – Acute vasoreactivity testing • Exercise capacity – 6-min walking test – Cardiopulmonary exercise testing • Analytical assessment: NT-proBNP

echocardiography. If there is a history of pulmonary thromboembolism, a ventilation-perfusion (V-Q) scan should be performed. If there are perfusion defects and the echocardiographic probability is intermediate or high, referral to an expert PH unit is mandatory to complete the evaluation for possible CTEPH. If the echocardiographic probability of PH is high or intermediate, left heart disease or respiratory disease that could justify it must be ruled out. If these conditions are ruled out, a diagnosis of PAH is possible, and the patient should be referred to an expert PH unit; where right heart catheterization (RHC) will be performed, specific studies to identify the subtype of PAH will be conducted, and the risk of mortality will be evaluated. Potential alarm signs (rapid progression of symptoms, signs of right heart failure, syncope, or presyncope with mild exertion) should be detected at any time of the diagnosis process, and if present, referral to an expert PH unit should be expedited [1].

This diagnostic process also applies to patients with CTD as they may present different types of PH (Fig. 78.1).

Screening for Pulmonary Hypertension

Screening for PAH in patients with SSc has been shown to detect PAH in a less advanced stage and is associated with better survival [3]. Current guidelines recommend the annual evaluation of the risk of having PAH in patients with SSc using screening algorithms that combine clinical features, echocardiography, pulmonary function tests (forced vital capacity (FVC) and carbon monoxide diffusing capacity (DLCO)), and NT-proBNP such as the DETECT algorithm [4]. Regular screening is highly recommended in patients with SSc presenting risk factors for PAH, which include breathlessness, longer disease duration, sicca symptoms, digital ulceration, older age, male sex, positive anti-centromere antibody profile, low DLCO, elevated FVC/DLCO ratio, and elevated NT-proBNP.

In patients with associated interstitial lung disease, pulmonary function testing is useful in distinguishing pulmonary vasculopathy from fibrotic alterations in patients who may associate both disorders. In patients with pulmonary fibrosis, FVC and DLCO decrease concurrently, being the ratio % predicted FVC/% predicted DLCO (%FVC/%DLCO) <1.4. If pulmonary vasculopathy is the most significant alteration, DLCO decreases out of proportion to FVC, and the %FVC/%DLCO ratio is >1.8. In patients presenting both disorders, the %FVC/%DLCO ratio ranges between 1.4 and 1.8.

Prognosis

The prognosis for untreated PAH is poor, particularly in patients with PAH-CTD. Accordingly, risk stratification for mortality should be performed at the initial assessment and during follow-up in all patients with PAH. For prognostic stratification, multidimensional parameters are considered,

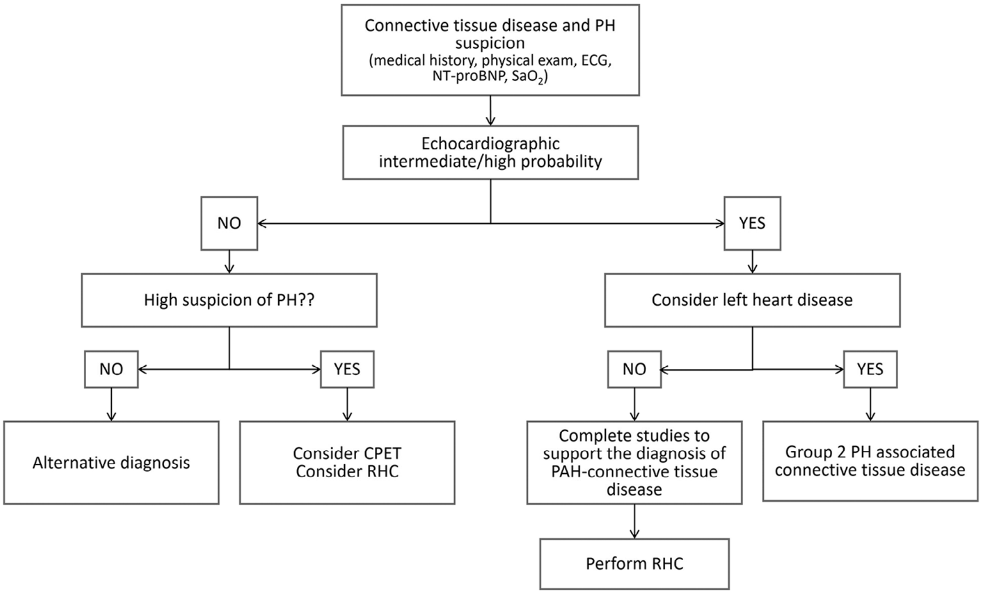

Connective tissue disease and PH suspicion
(medical history, physical exam, ECG, NT-proBNP, SaO2)
Echocardiographic intermediate/high probability
NO
YES
High suspicion of PH??
Consider left heart disease
NO
YES
NO
YES
Alternative diagnosis
Consider CPET
Consider RHC
Complete studies to support the diagnosis of PAH-connective tissue disease
Group 2 PH associated connective tissue disease
Perform RHC

Fig. 78.1 Diagnostic algorithm of pulmonary hypertension in patients with connective tissue diseases. *PH* pulmonary hypertension, *ECG* electrocardiogram, *NT-proBNP* N-terminal prohormone of brain natriuretic peptide, *SaO_2* oxygen saturation in arterial blood, *CPET* cardiopulmonary exercise test, *RHC* right heart catheterization, *PAH* pulmonary arterial hypertension

including clinical factors (signs of right heart failure, symptom progression, presence of syncope, and functional class), exercise tolerance (distance walked in the 6-min walk test or peak oxygen consumption and ventilatory efficiency in cardiopulmonary exercise testing), plasma BNP or NT-pro-BNP levels, echocardiographic findings (right atrial area, presence of pericardial effusion), magnetic resonance imaging, and hemodynamic measurements (cardiac index, indexed stroke volume, right atrial pressure, and mixed venous oxygen saturation) (Fig. 78.2) [1].

Treatment

General Measures

Patients should be advised to limit strenuous physical activity and avoid medications that can worsen PH (nasal decongestants, β-blockers). Supervised exercise training programs are effective in improving exercise tolerance and quality of life [5, 6]. In addition, vaccination for influenza, pneumonia, and SARS-CoV-2 coronavirus should be administered. Effective contraception should be recommended for women because the hemodynamic burden of pregnancy, especially in the immediate postpartum period, is poorly tolerated and can lead to maternal death in over 30% of cases [1].

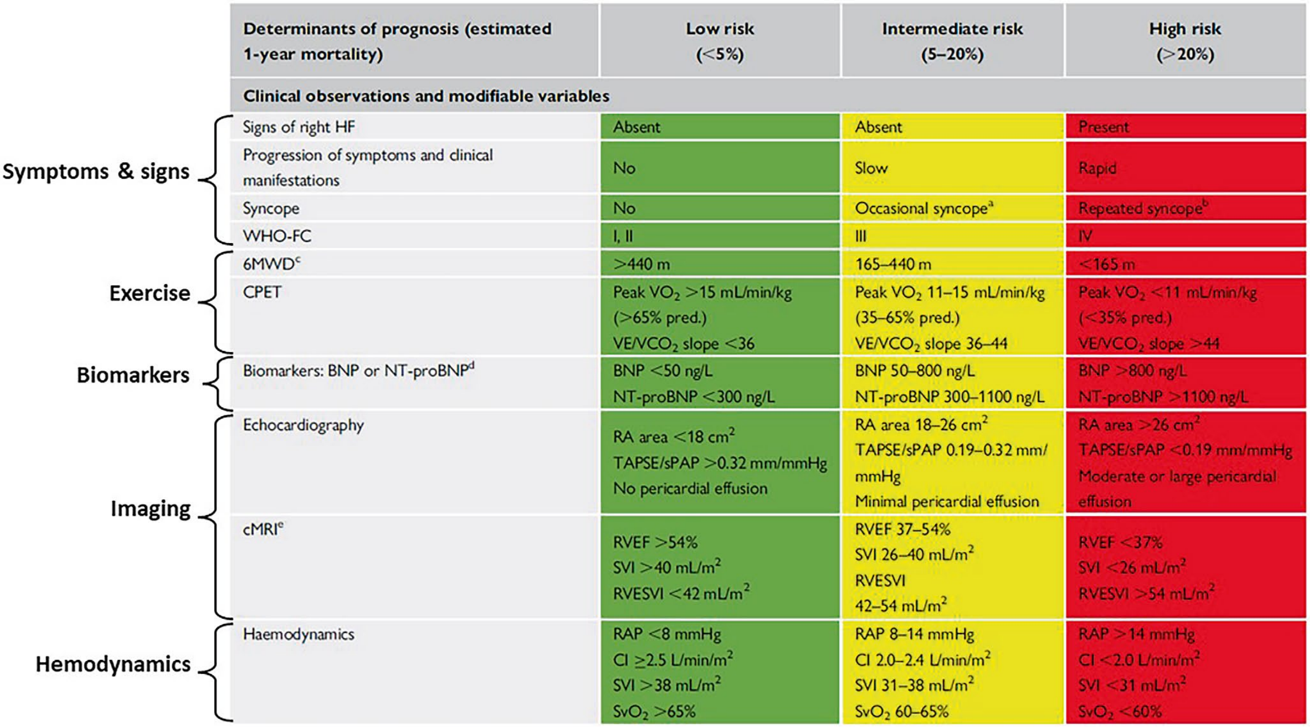
Pharmacological Treatment

Pharmacological treatment of patients with PAH-CTD is analogous to that of idiopathic PAH, although with some peculiarities. Immunosuppressive therapy with glucocorticosteroids and cyclophosphamide provides clinical improvement in patients with SLE- or MCTD-associated PAH, while it is not recommended in PAH-SSc. In PAH-SSc, oral anticoagulation is not recommended because of an increased risk of bleeding, although anticoagulation with vitamin K antagonists is recommended in PAH-CTD with a thrombophilic predisposition (antiphospholipid syndrome).

Calcium channel blockers, which are indicated in patients with idiopathic PAH who demonstrate a significant response in the pulmonary vasoreactivity testing [7], are not used in patients with PAH-CTD, as this vasodilator response is not usually observed in patients with PAH-CTD.

Pulmonary Arterial Hypertension Therapies

Pulmonary arterial hypertension therapies include drugs that act on endothelial function, exerting vasodilatory and potentially antiproliferative effects. There are five types of PAH therapies: prostacyclin analogs, prostacyclin receptor agonists, endothelin receptor antagonists, phosphodiesterase-5 (PDE-5) inhibitors, and soluble guanylate cyclase (sGC) stimulators.



	Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
	Clinical observations and modifiable variables			
Symptoms & signs	Signs of right HF	Absent	Absent	Present
	Progression of symptoms and clinical manifestations	No	Slow	Rapid
	Syncope	No	Occasional syncope[a]	Repeated syncope[b]
	WHO-FC	I, II	III	IV
Exercise	6MWD[c]	>440 m	165–440 m	<165 m
	CPET	Peak VO_2 >15 mL/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 mL/min/kg (35–65% pred.) VE/VCO_2 slope 36–44	Peak VO_2 <11 mL/min/kg (<35% pred.) VE/VCO_2 slope >44
Biomarkers	Biomarkers: BNP or NT-proBNP[d]	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–800 ng/L NT-proBNP 300–1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
Imaging	Echocardiography	RA area <18 cm^2 TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion	RA area 18–26 cm^2 TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion	RA area >26 cm^2 TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion
	cMRI[e]	RVEF >54% SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37–54% SVI 26–40 mL/m^2 RVESVI 42–54 mL/m^2	RVEF <37% SVI <26 mL/m^2 RVESVI >54 mL/m^2
Hemodynamics	Haemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m^2 SVI >38 mL/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 L/min/m^2 SVI 31–38 mL/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 L/min/m^2 SVI <31 mL/m^2 SvO_2 <60%

Fig. 78.2 Risk stratification in pulmonary arterial hypertension. *HF* heart failure, *WHO-FC* World Health Organization functional class, *6MWD* 6-min walking distance, *CPET* cardiopulmonary exercise testing, *VO_2* oxygen uptake, *VE/VCO_2* ventilatory equivalent for carbon dioxide, *BNP* brain natriuretic peptide, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *RA* right atrium, *TAPSE* tricuspid annular plane systolic excursion, *sPAP* systolic pulmonary arterial pressure, *cMRI* cardiac magnetic resonance imaging, *RVEF* right ventricular ejection fraction, *SVI* stroke volume index, *RVESVI* right ventricular end-systolic volume index, *RAP* right atrial pressure, *CI* cardiac index, *SvO_2* mixed venous oxygen saturation. [a]Occasional syncope during heavy exercise or occasional orthostatic syncope in a stable patient. [b]Repeated episodes of syncope even with little or regular physical activity. [c]Observe that 6MWD is dependent upon age, height, and burden of comorbidities. [d]BNP and NT-proBNP cut-off levels have been updated. [e]cMRI parameters. (Adapted from the 2022 European Society of Cardiology/European Respiratory Society Guidelines for the diagnosis and treatment of pulmonary hypertension [1])

Prostacyclin Analogs

Prostacyclin is a naturally occurring substance synthesized by the endothelium with vasodilatory and antiproliferative properties. Synthetic prostacyclin (epoprostenol) [8, 9] and analog preparations (iloprost, treprostinil) [10, 11] are available. Prostacyclin analogs prolong survival, improve pulmonary hemodynamics, increase exercise tolerance, and alleviate symptoms in patients with PAH.

Epoprostenol must be administered via continuous intravenous infusion due to its extremely short half-life (3–5 min), using a continuous infusion pump connected to a permanent central venous catheter. Effective doses range from 20 to 40 ng/kg of body weight per minute. Adverse effects are mainly related to the method of administration, including pump malfunction, catheter infections, and venous thrombosis. Abrupt discontinuation of the drug infusion can be fatal. The most common side effects are jaw pain, headache, skin erythema, diarrhea, and joint pain.

Iloprost has a slightly longer half-life than epoprostenol and can be administered intravenously or by inhalation. Nebulized iloprost is administered in repeated sessions every 4 h at doses of 2.5–5 μg per session. The most important side effect is the possibility of syncope.

Treprostinil can be administered subcutaneously, intravenously, orally, or by inhalation. Subcutaneous administration is most common at doses ranging from 20 to 80 ng/kg of body weight per minute. The most common adverse effect is erythema and pain at the subcutaneous catheter insertion site.

Prostacyclin Receptor Agonists

Selexipag is an orally administered drug that delays clinical deterioration. It is used at doses between 800 and 1600 μg every 12 h depending on tolerance. Common side effects are similar to those of prostacyclin agents.

Endothelin Receptor Antagonists

Endothelin-1 (ET-1) is an endothelium-synthesized peptide with potent vasoconstrictor and mitogenic effects, binding to both type A and B receptors. The action on both receptors in smooth muscle cells results in the deleterious effects of ET-1. However, the binding of ET-1 to type B receptors present in endothelial cells has vasodilatory and antiproliferative effects. Endothelin receptor antagonists (ERAs) are bosentan, ambrisentan, and macitentan, which are administered orally. Bosentan and macitentan are administered at doses of 125 mg every 12 h and 10 mg every 24 h, respectively. Ambrisentan is administered at doses of 5 or 10 mg per day. Endothelin receptor antagonists improve symptoms, exercise tolerance, and right ventricular function in PAH. With macitentan, a delay in clinical worsening has also been demonstrated. The most common adverse effect is elevated liver transaminases, requiring regular monitoring.

Phosphodiesterase-5 Inhibitors

PDE-5 inactivates intracellular cyclic guanosine monophosphate (cGMP), so its inhibition increases intracellular cGMP concentration, causing vasodilation. PDE-5 is highly expressed in pulmonary vessels. Drugs acting in this pathway are sildenafil and tadalafil. Sildenafil is administered orally at doses of 20 mg every 8 h, although doses of up to 80 mg every 8 h can also be effective. Tadalafil is administered at a dose of 40 mg per day. PDE-5 inhibitors improve functional class, hemodynamic profile, and exercise tolerance. The most common side effects are hypotension, headache, and dyspepsia [12].

Soluble Guanylate Cyclase Stimulators

Soluble guanylate cyclase (sGC) catalyzes the formation of cGMP from GTP. sGC stimulators promote cGMP formation independently of NO. Riociguat acts through this pathway and is administered orally at doses of 2.5 mg every 8 h with initial uptitration. Riociguat improves symptoms, exercise tolerance, and right ventricular function in PAH and CTEPH. The most common adverse event is elevated liver transaminases, requiring regular monitoring.

Supportive Measures

Supportive measures are aimed at treating complications of the disease, primarily right heart failure and hypoxemia. Treatment of right heart failure includes a low-salt diet and diuretics. Diuretics are indicated if there are signs of right ventricular failure but should be used cautiously as excessive diuresis can lead to inadequate right ventricular filling and compromise its function. Patients with arterial hypoxemia may benefit from supplemental oxygen [13].

Invasive Procedures

Lung transplantation is reserved for patients with PAH in functional class III-IV who do not respond to optimal medical treatment, including parenteral prostacyclin administration. Bilateral lung transplantation is usually performed. Connective tissue disease should not be considered a contraindication for lung transplantation, although careful evaluation is required with a special focus on gastroesophageal reflux disease and cardiac, renal, and cutaneous involvement.

Atrial septostomy is a palliative procedure that creates an intracardiac shunt from the right atrium to the left atrium, aimed at reducing right ventricular filling pressures in patients with severe right heart failure unresponsive to medical treatment. The right-to-left shunt worsens arterial oxygen, so candidates must have an oxygen saturation >90% while breathing ambient air.

Treatment Algorithm

Figure 78.3 schematically depicts the treatment algorithm for patients with PAH based on their risk. Given the low prevalence of PAH, the severity of the disease, and the potential need for complex drug administration, it is recommended that these patients be managed in specialized units experienced in the disease. Treatment includes general measures and pharmacological therapy. In patients with intermediate or low risk, treatment is initiated with the combination of an ERA and a PDE-5 inhibitor. In patients with cardiorespiratory comorbidity, treatment will start with only one of these agents. In high-risk patients, parenteral prostacyclin will be added to the two indicated drugs. The therapeutic goal is to have the patient in a low-risk clinical condition, so regular follow-up is necessary, starting at 3–4 months after treatment initiation. If, in the follow-up evaluation, the patient does not achieve a low-risk profile, treatment must be intensified, with an oral drug in case of intermediate-low risk or adding a parenteral prostanoid in case of intermediate-high or high risk.

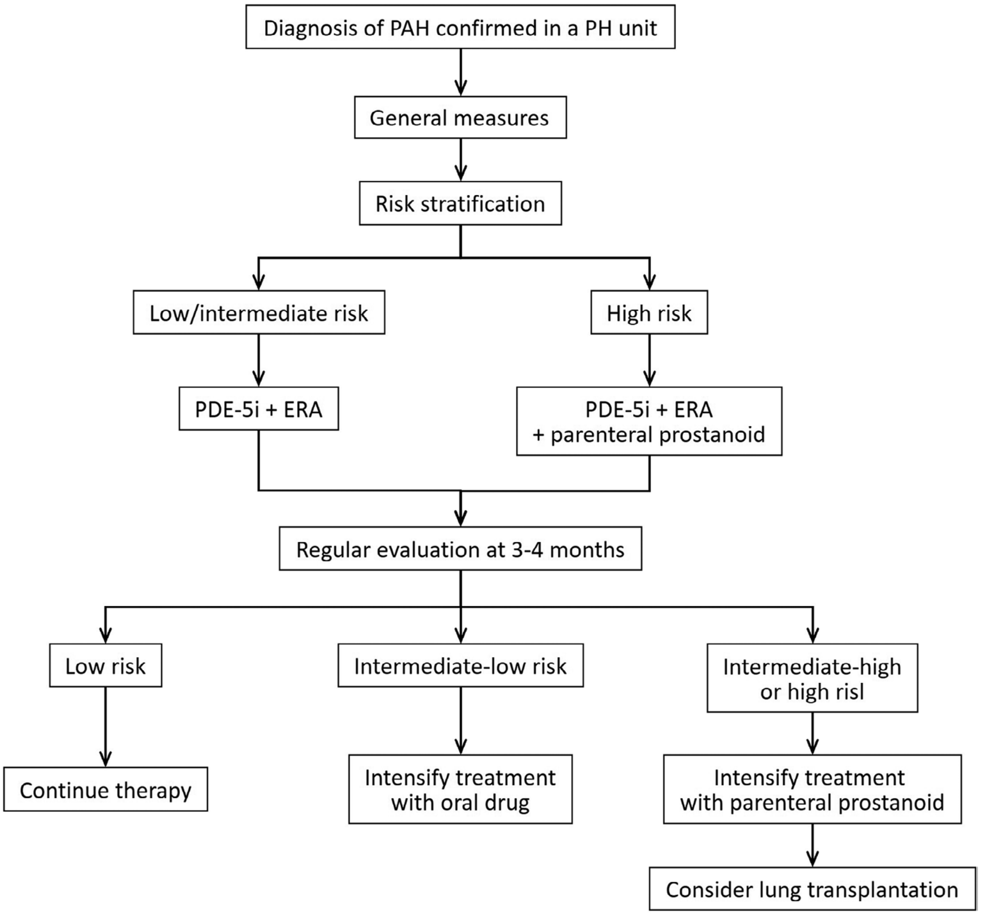

Diagnosis of PAH confirmed in a PH unit
General measures
Risk stratification
Low/intermediate risk
High risk
PDE-5i + ERA
PDE-5i + ERA
+ parenteral prostanoid
Regular evaluation at 3-4 months
Low risk
Intermediate-low risk
Intermediate-high
or high risl
Continue therapy
Intensify treatment
with oral drug
Intensify treatment
with parenteral prostanoid
Consider lung transplantation

Fig. 78.3 Treatment algorithm for pulmonary arterial hypertension. *PAH* pulmonary arterial hypertension, *PH* pulmonary hypertension, *PDE-5i* phosphodiesterase-5 inhibitor, *ERA* endothelin receptor antagonist

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Part X

Neurological Autoimmune Diseases

Multiple Sclerosis

79

J. M. Cabrera-Maqueda and Y. Blanco

Abstract

Multiple sclerosis (MS) is a prevalent chronic disorder characterized by inflammation and demyelination in the central nervous system (CNS), leading to varying degrees of axonal and neuronal damage. It affects approximately 2.8 million people worldwide, predominantly young adults. The underlying cause involves a breakdown in immune tolerance, although no single autoantigen or autoantibody has been definitively linked to MS. The disease manifests primarily in two forms: relapsing-remitting MS (RRMS) and progressive MS (PMS), with the latter marked by a gradual accumulation of disability.

Diagnostic criteria for MS have evolved over time to incorporate advances in understanding and diagnostic techniques. Historical criteria, dating back to the nineteenth century, initially focused on clinical symptoms but later emphasized the importance of imaging findings, such as dissemination in space and time. The McDonald criteria, introduced in 2001 and subsequently revised, streamlined the diagnostic process by integrating clinical and MRI evidence. These criteria prioritize objective demonstration of CNS lesions and dissemination in space and time, crucial for accurate diagnosis.

However, distinguishing MS from other conditions that mimic its symptoms remains essential. Disorders like neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) can present similarly but require distinct management approaches.

While there is no cure for MS, various disease-modifying therapies (DMTs) aim to reduce relapses and slow disability progression, with early treatment showing promise in limiting long-term disability. Moreover, lifestyle factors such as sunlight exposure, vitamin D levels, and smoking cessation may influence MS risk.

In conclusion, understanding the complexities of MS diagnosis and treatment is critical in improving outcomes and quality of life for individuals affected by this debilitating condition.

Keywords

Neurology · Neuroimmunology · Demyelinating disorders · Multiple sclerosis · Diagnostic criteria

Description of Multiple Sclerosis

Multiple sclerosis (MS) is a chronic disorder marked by inflammation and demyelination of the central nervous system (CNS) associated with varying levels of axonal and neuronal damage. It is the most common neurological disease of young adults, and a total of 2.8 million people are estimated to live with MS worldwide (35.9 per 100,000 population) [1]. A breakdown in immune tolerance is posited to result in the persistence of autoreactive lymphocytes that gain access to the CNS and start the pathogenic cascade. However, neither a single autoantigen nor an autoantibody has been unequivocally associated with the origin of MS [2].

The disease may initially present with (less often) or evolve into (more common) a relentless progressive decline of neurologic functioning, commonly affecting locomotion, bladder function, and cognition (Table 79.1). Therefore, two main forms of multiple sclerosis can be distinguished: relapsing-remitting forms (RRMS) and pro-

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gressive forms (PMS). About 85% of patients initially have periodic relapses followed by complete or partial remission known as RRMS. A relapse or clinical attack is an episode of CNS symptoms with a sudden or moderately gradual beginning of symptoms which quickly reach their most intense point within a span of 2–3 weeks. Pathologically, relapses represent an acute inflammatory demyelination event with or without axonal injury, and MRI may show new T2-hyperintense or contrast-enhancing lesions. The main syndromes typical of MS are shown in Table 79.2.

Table 79.1 Manifestations of multiple sclerosis

Symptoms and signs	Total (%)
Sensory in limbs	31
Visual loss	16
Weakness	13
Diplopia	7
Gait disturbance	5
Balance problems	3
Sensory in face	3
Lhermitte sign[a]	2
Vertigo	2
Bladder problems	1
Limb ataxia	1
Acute transverse myelopathy	1
Pain	<1
Other	3
Polysymptomatic onset	14

[a] Lhermitte sign: electric shock-like sensations that run down the back and/or limbs upon flexion of the neck. Modified from Richards and colleagues [3]

PMS is characterized by a gradual accumulation of neurological symptoms and subsequent disability accumulation, presented since onset (primary progressive MS, PPMS) or mostly 10 to 15 years after having had a relapsing-remitting course (secondary progressive MS, SPMS). The progression corresponds to axonal injury or loss and might not be reflected in brain MRI, except for atrophy [5].

No specific serological MS biomarkers exist for MS. Testing for AQ4-IgG (specific biomarker for neuromyelitis optica spectrum disorder) or MOG-IgG (MOG antibody-associated disease) is not recommended in patients with typical clinical and imaging evidences of MS [6].

Ancillary test for MS diagnosis and to rule out other conditions that can mimic the disease are shown in Table 79.3.

Table 79.2 Typical syndromes features that are typical and atypical for MS. Adapted from Miller and colleagues [4]

Optic nerve	
Typical features • Optic neuritis in one eye • Mild pain in eye movement • Reduced visual acuity and reduced color vision • Normal disc or mild disc swelling • Improvement begins within 3 weeks from onset • Afferent pupil defect	**Atypical features** • Optic neuritis in both eyes at the same time • Painless or very severe pain • No perception of light • Severe haemorrhages and exudates • Extended loss of vision • Vitritis and neuroretinitis • Photophobia
Brainstem or cerebellum	
Typical features • Bilateral internuclear ophthalmoplegia • Ataxia and gaze-evoked nystagmus • Sixth nerve palsy (in patients aged 20–40 years) • Paroxysmal phenomena (occurring for at least 24 h) • Multifocal signs (e.g., facial sensory loss and vertigo)	**Atypical features** • Complete external ophthalmoplegia • Vascular territory signs • Isolated trigeminal neuralgia • Progressive trigeminal sensory neuropathy • Movement disorders • Fluctuating ocular or bulbar weakness, or both
Spinal cord	
Typical features • Incomplete transverse myelitis • Lhermitte's syndrome • Sphincter symptoms • Asymmetric limb weakness • Deafferented hand • Progression to nadir between 4 h and 21 days	**Atypical features** • Complete transverse myelitis • Complete Brown-Séquard syndrome • Cauda equina syndrome • Anterior spinal artery territory lesion • Localised or radicular spinal pain • Progressive and symmetrical spastic paraparesis or progressive sensory ataxia (from involvement of posterior columns) • Sharp level to all sensory modalities • Areflexia
Cerebral hemispheres	
Typical features • Hemiparesis • Hemisensory disturbance	**Atypical features** • Encephalopathy • Epilepsy • Cortical blindness

Table 79.3 Ancillary test for MS diagnosis. CRP: C-reactive protein

Cerebrospinal fluid	
Although cerebrospinal fluid (CSF) examination is not mandatory, it is strongly recommended in the following situations: when clinical and MRI evidence is insufficient to support a diagnosis of MS; when there is a presentation other than a typical clinically isolated syndrome, including a progressive course at onset (PMS); when clinical, imaging, or laboratory features are atypical of multiple sclerosis; and in populations in which MS is less common (eg, children, older individuals, or non-White populations)	• Total protein/albumin quotient: normal, rarely slightly elevated • CSF-to-serum glucose ratio: normal • CSF leukocyte count: less than 50 cells/uL in 98% of MS patients • Cytology: dominated by lymphocytes (90% of cells) • Immunoglobulins quantitative: IgG index, the relationship between CSF IgG and serum IgG. Increased ($\geq$ 0.7) in 75% of patients[a] • Immunoglobulins qualitative: oligoclonal IgG bands (OCBs). More than two OCBs with pattern II (OCB only in CSF) or pattern III (OCB in CSF and serum with additional bands in CSF) indicate intrathecal synthesis, and both of them are considered positive results. 95% of MS patients are positive and 85% of patients with CIS[a][7]
Blood tests	
While there are no definitive blood tests for diagnosing MS, they can rule out other conditions that may mimic MS symptoms	• Complete blood count • Renal and liver function tests • CRP and ESR • Vitamin B12, folate, and vitamin D levels • Thyroid function tests • RF, ANA • Viral serology (anti-HIV, anti-HCV, HbsAg, anti-Hbs) • ANA and ENA profile
Brain and spinal cord MRI	
A lesion in multiple sclerosis is defined as an area of focal hyperintensity on a T2-weighted (T2, T2-FLAIR, or similar) or a proton density (PD)-weighted sequence. Typical MS lesions are round to ovoid in shape and range from a few millimeters to more than one or two centimeters in diameter, and they tend to affect specific white matter regions	• Periventricular lesions • Juxtacortical and cortical lesions • Infratentorial lesions • Spinal cord
Secondary tests	
Evoked potentials	• Abnormal visual evoked responses: 50–90% of patients • Abnormal brainstem auditory evoked responses: 20–55% • Abnormal somatosensory evoked potentials: 50% [8]
OCT: Thinning of the peripapillary retinal nerve fiber layer (pRNFL) or the ganglion cell layer plus inner plexiform layer (GCIPL) in eyes without a prior history of optic neuritis has been associated with disability progression in patients with MS or a clinically isolated syndrome. In addition, OCT testing may be useful for demonstrating objective evidence of retinal nerve fiber layer loss in patients who have a history consistent with optic neuritis but otherwise have a normal examination and brain imaging	• Thinning of the peripapillary retinal nerve fiber layer (pRNFL) • Thinning of the ganglion cell layer plus inner plexiform layer (GCIPL)

ESR erythrocyte sedimentation rate, *RF* rheumatoid factor, *ANA* antinuclear antibodies, *ENA* antibodies against extractable nuclear antigens, *OCT* optical coherence tomography

[a] Paired CSF and serum samples are required for accurate interpretation. In most hospitals, the IgG index is ready within a day. The analysis of OCB, in contrast, is more time-consuming

Diagnostic Criteria for Multiple Sclerosis

Diagnostic criteria for MS have evolved to reflect advances in our understanding of the disease and the development of new diagnostic techniques and from purely clinical considerations to increasing dependency upon imaging of the central nervous system.

Historical Review

In the nineteenth century, Jean-Martin Charcot deserves credit for being the first to delineate diagnostic criteria for MS identifying common neurological symptoms, such as optic neuritis and internuclear ophthalmoplegia. No further attempts were made to characterize MS until 1906 by Otto

Marburg and Sydney Allison in 1931, both suggesting the combination of clinical evidence of involvement of different areas of the central nervous system (CNS), which was the first hint of dissemination in space.

It was in 1954 that the first true diagnostic scheme appeared, published by Allison and Miller, describing three categories: early, probable, and possible disseminated sclerosis. However, these criteria showed great variability in diagnostic accuracy, ranging from 91.7 to 2.8% for cases of "pure" MS, which strongly underscored the importance of establishing formal diagnostic criteria for MS to ensure the validity of published epidemiological studies or any therapeutic trial conducted. A major step in that direction occurred in 1965, when Broman et al. first considered the electrophoretic examination of CSF protein, the precursor of oligoclonal bands, and they clearly stated the twin principles of dissemination in time (DIT) and dissemination in space (DIS) that to this day remain the fundamental criteria for the diagnosis of MS.

The Schumacher et al. Criteria 1965. One of the most important features was that the authors wisely described only the single category of clinically definite MS based on objective signs of dysfunction of the central nervous system (symptoms not acceptable) and evidence of damage to two or more sites, reflecting the concept of DIS.

The McAlpine, Lumsden, and Acheson Criteria. In 1972, these authors avoided the classification of definite MS, listing only latent probable, probable, and possible MS. They accepted a history of remitting symptoms in the past with the presence of physical signs. Nevertheless, the proposed scheme relied heavily on subjective judgment.

The Poser et al. Criteria. Poser Criteria established two major groups, definite and probable, each with two subgroups, clinical and laboratory supported. Clinically definite MS refers to the evidence of two relapses (DIT) together with clinical or paraclinical evidence of lesions in two places within the CNS (DIS).

Additionally, for the first time, clear definitions of the terminology were established. An attack (bout, episode, exacerbation) could be characterized solely by symptoms and had to endure for a minimum of 24 h. The term "paraclinical" evidence was introduced to encompass the findings from evoked response studies and neuroimaging. A new category called "laboratory supported" was introduced, specifically pertaining to the examination of cerebrospinal fluid (CSF) for oligoclonal bands (OCBs) and increased production of immunoglobulin G (IgG). However, these criteria failed to diagnose up to 26.5% of patients and did not take into account primary progressive MS [9].

The McDonald et al. Diagnostic Criteria. In 2001, the International Panel on the Diagnosis of MS published the first McDonald criteria [10]. They aimed to simplify and speed up the diagnosis process by allowing for an earlier diagnosis based on clinical and MRI evidence. The focus also remained on the objective demonstration of dissemination of lesions in both dissemination in time (DIT) and dissemination in space (DIS), as a chronic and multifocal CNS disease. The main contributions were to facilitate the diagnosis of MS in patients with a variety of presentations, including "monosymptomatic" disease suggestive of MS (clinically isolated syndrome, CIS), a disease with a typical relapsing-remitting course (RRMS), and disease with insidious progression, without clear attacks and remissions (primary progressive MS, PPMS). Although the diagnosis could still be made on clinical grounds alone, MRI could support, supplement, or even replace some clinical criteria. Previously used terms such as "clinically definite" and "probable MS" were no longer recommended. The McDonald criteria have been revised several times (in 2005, 2010, and 2017) to increase sensitivity and specificity, further improving diagnostic accuracy and allowing for better counseling of patients and earlier treatment.

In 2001 and 2005 [11] versions, the DIS by MRI relied on the presence of three of four of the following (Barkhof–Tintoré MRI Criteria): ≥ 9 T2-hyperintense lesions or 1 gadolinium-enhancing lesion, ≥3 periventricular lesions, ≥1 juxtacortical, and ≥ 1 infratentorial lesion (not included spinal cord). A spinal cord lesion could be considered equivalent to a brain infratentorial lesion to reach the required number of T2 lesions. The main contribution of the 2005 revision of McDonald criteria was to show DIT by detection of a new T2 lesion if it appeared at any time and not after at least 3 months, compared with a reference scan, which allowed anticipating the diagnosis.

The main contributions of the 2010 revision of the McDonald criteria [12] were the simplification of MRI diagnostic criteria for DIS by the implementation of Swaton criteria (in place of Barkhof–Tintoré MRI criteria) that require the presence of only 1 lesion in at least 2 of 4 areas of the CNS (periventricular, cortical/juxtacortical, infratentorial, spinal cord; if a subject had a brainstem or spinal cord syndrome, the symptomatic lesions was excluded from the criteria and did not contribute to lesion count). In Fig. 79.1, these new DIS criteria demonstrated a higher sensitivity and similar accuracy (sensitivity 85.9% (76.6–92.5), specificity 59.4% (50.1–68.1), and accuracy 70.2% (63.5–76.3)) [14]. Another important contribution was that the simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time allowed DIT without the need for additional MRI.

The latest revision of McDonald criteria was done in 2017 and continues to be based on four principles to confirm the diagnosis of MS [15]: (1) the identification of a syndrome "typical" of MS-related demyelination, (2) objective evidence of central nervous system (CNS) involvement, (3) demonstration of dissemination in space and in time, and (4) "no better explanation" other than MS.

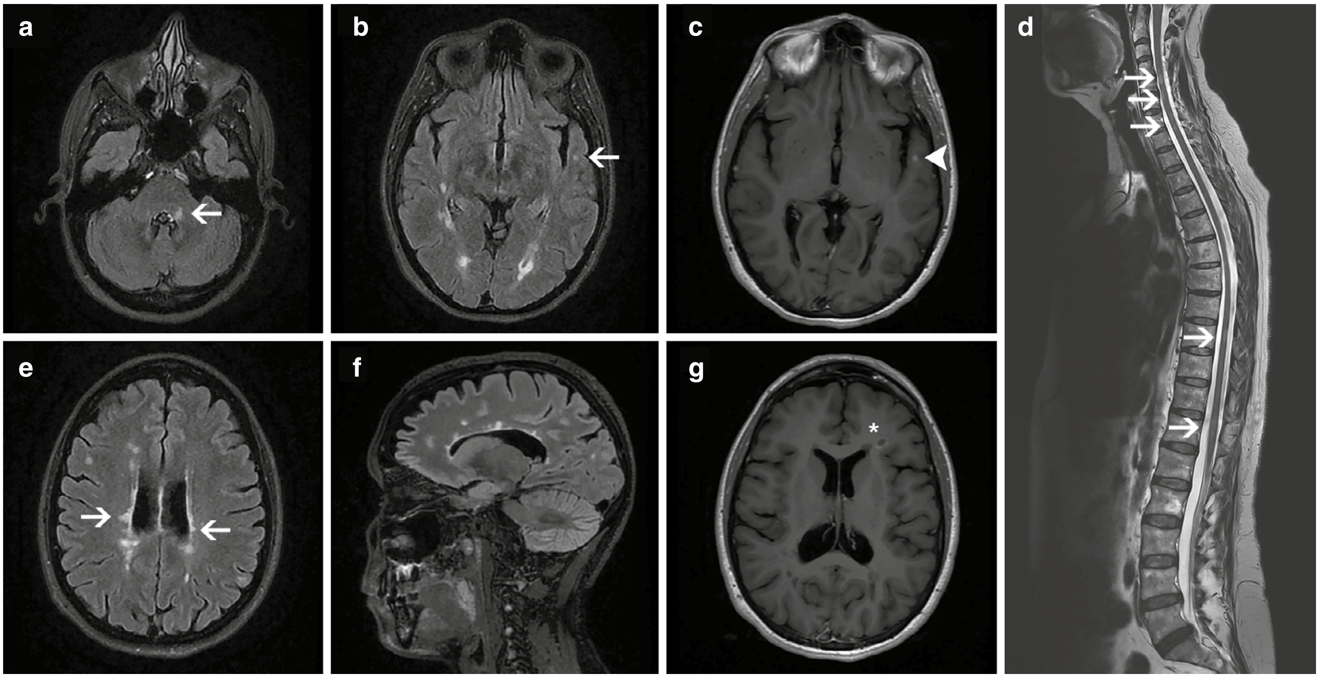


Fig. 79.1 Axial flair (**a**, **b**, **e**, **f**), T2-weighted (**d**), and gadolinium-enhanced T1-weighted (**c**, **g**) brain and spinal cord MRI of a patient with CIS. (**a**) Infratentorial lesions. An infratentorial lesion is defined as a T2-hyperintense lesion in the brainstem, cerebellar peduncles, or cerebellum. (**b**) Juxtacortical or cortical lesions. A juxtacortical lesion is located abutting, i.e., in direct contact with, the cortex without intervening normal white matter. The image shows a juxtacortical lesion (arrow) involving the U-fibers in the left temporal lobe with contrast nodular contrast enhancement (**c**, arrowhead). Cortical lesions are defined as focal abnormalities completely within the cortex or spanning the cortex and subjacent white matter, and they are considered a distinctive feature of MS. (**d**) Spinal cord lesions. MS spinal cord lesions are often multiple (mostly cervical, also thoracic and lumbar), covering less than two vertebral segments and usually less than half of the cord area (mainly in the lateral or dorsal columns). (**e**) Periventricular lesions. Lesions abutting (touching) the ventricles and located in the corpus callosum are included except for those located in the deep grey matter (e.g. caudate nucleus or thalamus). (**f**) "Dawson's fingers". Periventricular MS lesions are typically distributed along the deep medullary veins (perivascular), thus having their main axis perpendicular to the lateral ventricles. They have an ovoid shape on the axial plane and are generally defined as "Dawson's fingers" [13]. (**g**) Gadolinium-enhancing lesions. Enhancement in new inflammatory demyelinating lesions is a transient characteristic (usually lasting <4 weeks). Enhanced MS lesions are often nodular, but larger ones can exhibit "open-ring" enhancement (open toward the side that abuts ventricles or grey matter) or closed-ring enhancement, as depicted in the image. Subcortical lesions like the one shown (asterisk), although taken into account for the MS lesion load, are not considered to meet the diagnostic criteria

Typical Syndromes

The evaluation for a diagnosis of MS begins with an assessment of whether a patient has symptoms suggestive of an inflammatory demyelinating disorder of the CNS. This first relapse is known as clinically isolated syndromes (CISs). The term CIS is usually used for a situation in which a young adult (between the ages of 20 and 45) experiences a CNS neurological syndrome. Furthermore, there should not be any observable clinical signs of encephalopathy, fever, or infection. For it to be classified as a CIS, the episode should endure for a minimum of 24 h, always isolated in time (i.e., monophasic), and it is usually isolated in space (i.e., monofocal in a unique area of the CNS).

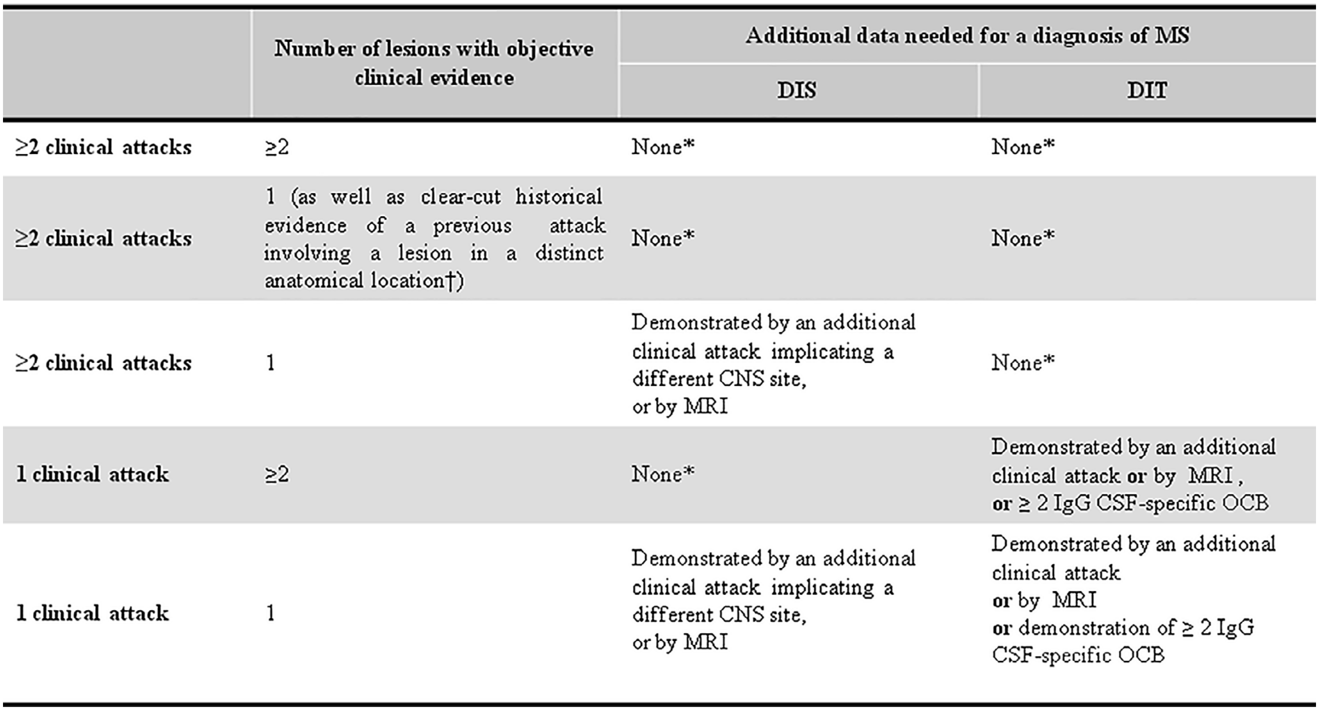
Objective Evidence

Objective clinical evidence on physical examination of at least one CNS lesion corresponding to the presentation of an attack typical for MS-related demyelination is also necessary to fulfill MS diagnostic criteria.

Dissemination in Space and Time

Patients with ≥2 clinical attacks and ≥ 2 lesions with objective clinical evidence or those with ≥2 clinical attacks and 1 lesion with objective clinical evidence (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location) do not require additional data for a diagnosis of MS (Fig. 79.2). However, unless an MRI is not possible, a brain MRI should be obtained in all patients for whom the diagnosis of MS is being considered.

In cases where only 1 clinical attack is observed, additional data through a combination of clinical and MRI evidence for DIS and DIT are required to establish a diagnosis of MS (Fig. 79.2).



	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of MS	
		DIS	DIT
≥2 clinical attacks	≥2	None*	None*
≥2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location†)	None*	None*
≥2 clinical attacks	1	Demonstrated by an additional clinical attack implicating a different CNS site, or by MRI	None*
1 clinical attack	≥2	None*	Demonstrated by an additional clinical attack **or** by MRI, **or** ≥ 2 IgG CSF-specific OCB
1 clinical attack	1	Demonstrated by an additional clinical attack implicating a different CNS site, or by MRI	Demonstrated by an additional clinical attack **or** by MRI **or** demonstration of ≥ 2 IgG CSF-specific OCB

Fig. 79.2 2017 McDonald criteria for diagnosis of multiple sclerosis. *MS* multiple sclerosis, DIS: dissemination in space, *DIT* dissemination in time, *CNS* central nervous system, *MRI* magnetic resonance imaging, *CSF* cerebrospinal fluid, *OCB* oligoclonal band. *No additional tests are required to demonstrate DIS and DIT. However, unless an MRI is not possible, a brain MRI should be obtained in all patients for whom the diagnosis of MS is being considered. †Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed. (Adapted from Thompson and colleagues [15])

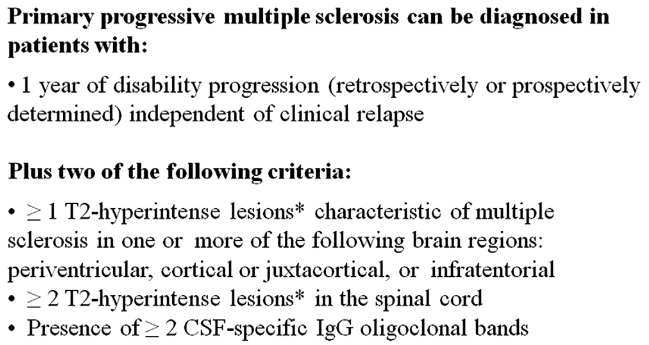
DIS can be demonstrated by an additional clinical attack implicating a different CNS site or by MRI (simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI).

DIT can be demonstrated by an additional clinical attack or by MRI (simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI). As CSF OCBs are an independent predictor of the risk of a second attack, they can be used to fulfill DIT in the case of a typical CIS, fulfillment of clinical or MRI criteria for DIS, and no better explanation for the clinical presentation.

"No Better Explanation": The Differential Diagnosis of Relapsing-Remitting Multiple Sclerosis

A variety of disorders may present with objective evidence of a syndrome typical for MS and demonstrate clinical or radiographic dissemination in space and dissemination in time, thus appearing to fulfill MS diagnostic criteria. Disorders such as neuromyelitis optica spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD), neurosarcoidosis, and CNS manifestations of the systemic, rheumatologic, and oncologic disease may be mimickers of MS. Thoughtful assessment for such red flags may avoid a misdiagnosis of MS. Noninflammatory conditions may also be mistaken for a typical presentation of multiple sclerosis. Knowledge of broad red flags suggesting a structural, functional, metabolic, infectious, neoplastic, or other diseases may lead to a specific alternative diagnosis.

Particularly, approximately 10% to 15% of patients with MS have a progressive course from the onset of symptoms [16]. The diagnostic criteria for PMS differ from the criteria for RRMS. A small proportion of patients with PPMS may have infrequent attacks or relapses. The diagnosis of PPMS first requires confirmation of at least 1 year of gradual disability progression, independent of any disability associated with a clinical relapse, determined either retrospectively or prospectively. In addition to 1 year of progression, primary progressive MS diagnostic criteria require fulfillment of other requirements (Fig. 79.3) [15].



Primary progressive multiple sclerosis can be diagnosed in patients with:

- 1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse

Plus two of the following criteria:

- ≥ 1 T2-hyperintense lesions* characteristic of multiple sclerosis in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial
- ≥ 2 T2-hyperintense lesions* in the spinal cord
- Presence of ≥ 2 CSF-specific IgG oligoclonal bands

Fig. 79.3 2017 McDonald criteria for diagnosis of multiple sclerosis in patients with a disease course characterized by progression from onset (primary progressive multiple sclerosis). #Unlike the 2010 McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required, and the combination of cortical and juxtacortical lesions to expand the concept of juxtacortical involvement. OCB: oligoclonal band. (Adapted from Thompson and colleagues [15])

Patients included in the studies on which the 2017 revisions to the McDonald criteria were predominantly White patients from Europe, the USA, and Canada who were between 11 and 50 years old. Therefore, the criteria should be applied with caution outside these cases [15].

The 2017 McDonald criteria are validated, and evidence-based criteria that show high sensitivity and accuracy in predicting the occurrence of a second clinical attack simplify the clinical use of MRI criteria and allow an earlier diagnosis and treatment of MS. Some concerns have been raised due to their low specificity [17–19]. However, their application is recommended only after alternative diagnoses have been carefully excluded.

There is no cure for MS, but from first subcutaneous IFNβ1b in 1993 until now, 16 disease-modifying therapies (DMT) are available for RRMS treatment. These DMTs aim to reduce the number of relapses, slow the progression of disability, and diminish the impact of MS on health-related quality of life. Selection of treatment requires a balance between the efficacy and safety profiles, which vary across treatments. High-efficacy DMTs are often associated with an increased risk of serious adverse events, but recent evidence suggests that early treatment with high-efficacy DMTs may lead to lower future disability [20]. For the PMS, the therapeutic options are more limited.

Low sunlight exposure, vitamin D deficiency, obesity, and smoking are factors with strong evidence for association with multiple sclerosis risk. Many infectious agents have been reported to be associated with multiple sclerosis risk; however, only Epstein-Barr virus infection has been consistently shown to be a risk factor [2].

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Myasthenia Gravis

80

Wakar Garra and Yair Levy

Abstract

Myasthenia gravis (MG) is an autoimmune disease that affects the post-synaptic area of the neuromuscular junction. Its hallmark is the weakness that worsens with activity. The incidence of MG has been increasing in recent decades ranging from 4.1 to 30 cases per million person-years, which is considered to be due to the aging population or unknown environmental factors.

The disease has several subtypes that differ slightly in their clinical characteristics, immunological markers, population distribution, and suitable treatments. The autoimmune nature of the disease is manifested by a decrease in the number of acetylcholine receptors in the muscle receptors, which makes the endplate potential lower than the threshold needed to activate muscle fiber action potential. Herein, we present a review of MG concentrating on the diagnosis.

Keywords

Myasthenia gravis · Diagnosis · Acetylcholine receptor · Autoantibodies to acetylcholine Receptor · Treatment

Introduction

Myasthenia gravis (MG) is an autoimmune disease affecting the post-synaptic side of the neuromuscular junction. MG has been known for more than 300 years, but only in recent decades has there been a better understanding of the disease's pathophysiology and its autoimmune nature, which leads to better treatments and a lower mortality rate [1]. The disease affects the neuromuscular junction leading to weakness in the ocular, facial, bulbar, limb, and respiratory muscles. The estimated prevalence of MG is 70–300 per million people worldwide [2].

The disease had been considered to affect predominantly females in the third to fourth decades of life but has shown a bimodal peak in males, in the third and sixth decades [3–5]. Overall, the incidence and prevalence of MG show little geographical variation [3–5]. There are no clear precipitating factors, but in some patients, disease onset has been related to an infection, emotional stress, surgery, trauma, hyperthyroidism, pregnancy, or exposure to drugs, especially antibiotics [6–10]. The mortality rate of uncontrolled disease is almost 2% [2].

Pathophysiology

The most prominent abnormality in MG is a decrease in the number of acetylcholine receptors [2, 5]. This decrease causes the endplate potential to be lower than the threshold needed to activate the muscle fiber action potential. The pathological mechanism responsible for generalized MG in about 85% of patients consists of autoantibodies directed against the acetylcholine receptor (AChR) on the post-synaptic membrane of the neuromuscular junction. These antibodies are IgG1 or IgG3 isotypes, capable of activating the complement system. The antibodies reduce the available acetylcholine receptors through three mechanisms: destruction of the muscle endplate, accelerated degradation of AChRs caused by cross-linkage of AChRs by divalent antibodies resulting in a temperature-dependent loss of AChRs, and direct blockade of AChRs by antibodies attached to acetylcholine binding. Muscle endplate destruction is probably the most important mechanism. It is complement-mediated and causes a distortion of the fold pattern of the post-synaptic membrane [2, 5].

There is a great deal of evidence implicating the thymus gland in the autoimmune derangement in MG. Neoplastic

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epithelial cells in thymomas express self-like antigens, including AChR-like, titin-like, and ryanodine receptor–like epitopes. Autoantibodies directed against muscle-specific tyrosine kinase (MuSK) adversely affect the maintenance of AChR clustering at the muscle endplate, leading to reduced numbers of functional AChRs. Up to 37% of patients with MG who are seronegative for anti-AChR antibodies have anti-MuSK antibodies. Autoantibodies directed against low-density lipoprotein receptor–related protein 4 (LRP4) are present in about 3–50% of double seronegative MG cases. Under normal circumstances, interactions between MuSK and LRP4 cause clustering of AChRs. MuSK antibodies are mainly IgG4. IgG4 antibodies do not activate the complement cascade. Therefore, complement inhibition will not be an effective treatment strategy in MuSK antibody-positive MG [2, 5].

Clinical Manifestations

MG is characterized by a painless weakness of striated muscles, which is more prominent with activity and improves with rest. Ocular manifestations (diplopia and ptosis) are usually the first symptoms to appear, in approximately 85% of patients [5, 11–14]. Dysphagia, dysarthria, or chewing difficulties is an initial symptom in a minority of patients (Table 80.1). Respiratory muscle weakness is a rare presentation of the disease but can be life-threatening requiring prompt intubation to maintain the airway. MG usually progresses to its maximum severity within 2 years of its appearance [5, 11–14].

MG can be categorized according to (1) course type (ocular or generalized), (2) age of onset (including before puberty, early onset before the age of 50 years, late onset after the age of 50 years), (3) antibody specificity (anti-AChR, anti-MuSK, anti-LRP4, seronegative), and (4) pathology of the thymus (including normal, thymitis, or para-neoplastic occurrence associated with thymoma) [5, 11].

Table 80.1 Distribution of weakness in myasthenia gravis

Only ocular	17%
Ocular and bulbar	13%
Mild	2%
Moderate/severe	11%
Ocular and limb	20%
Generalized	50%
Mild	2%
Moderate	14%
Severe	15%
Assisted ventilation	11%
Died despite ventilation	8%

MG Due to Antibodies Against AChR

The core clinical manifestations are fatigable muscle weakness, worsened by exertion that improves with rest. The most common presenting symptoms are ocular, with double vision and ptosis. Up to 80% of patients with ocular onset will go on to develop generalized symptoms, usually within 2 years of disease onset. Bulbar muscles are also frequently involved, resulting in flaccid dysarthria, dysphagia, and facial and jaw weakness. Axial weakness can also be present, with neck flexion weakness usually more common than weakness of neck extension. About 15%–20% of patients with AChR-MG develop respiratory weakness requiring mechanical ventilation (MG crisis). Early-onset MG appears before the age of 50. It has female predominance and anti-AChR antibodies and is usually correlated with a hyperplastic thymus gland. Thymectomy has been proven effective in improving clinical outcomes and minimizing the need for immunotherapy. Late-onset MG is defined by onset after the age of 50. It has a male predominance, and the thymus histology is usually normal. In addition to anti-AChR antibodies, these patients usually have antibodies to striated muscle proteins. The presence of these anti-muscle antibodies, particularly anti-ryanodine receptor antibodies, has been associated with more severe generalized weakness and frequent myasthenic crises [15].

Thymoma-Associated MG

Thymoma-associated MG appears equally in men and women and can occur at any age, with peak onset at the age of 50 years. The clinical presentation tends to be more severe, commonly with progressive generalized and oropharyngeal weakness. However, the long-term prognosis is similar to that of late-onset. MG patients with thymoma have high anti-AChR antibody titers, some have antibodies to titin, and some reports showed antibodies to additional paraneoplastic-associated antibodies. The removal of the thymoma usually cures the tumor but not the MG, which requires long-term immunosuppressive therapy [5, 11].

MuSK Antibody-Associated MG

Approximately 15% of patients with generalized MG have negative anti-AChR. Antibodies to MuSK are found in about 40% of these patients. The clinical presentation is similar to that of anti-AChR-positive MG, but patients commonly have atypical clinical features, such as selective facial, bulbar, neck, and respiratory muscle weakness and marked muscle atrophy, occasionally with relative sparing of the ocular muscles. Respiratory crises are more common. Disease onset in patients with anti-MuSK MG tends to be earlier, and patients are predominantly female. Thymus histology is usually normal [5, 11].

Double-Seronegative Generalized MG

Patients who are seropositive for both AChR and MuSK are rare. Presentation is similar to that of those positive for AChR antibodies in regard to the distribution of muscle weakness, severity, and response to treatment [5, 11].

Lrp4 Antibody–Associated MG

This version has a female predominance. Age at onset is variable, but patients tend to present before age 50. They can present with ocular or generalized MG, but the severity is overall milder in this subgroup [5, 11].

Diagnosis

The diagnosis of autoimmune MG remains clinical, with bedside tests and laboratory methods to confirm the disorder. Antibody tests are ordered first, followed in some patients by pharmacologic and electrodiagnostic tests [16].

The edrophonium (Tensilon, Enlon) test consists of administering edrophonium (a short-acting acetylcholinesterase inhibitor) and observing the patient for improvement. It has been used to diagnose MG diagnosis since the 1950s. It is an objective and reliable test, with a 71.5–95% sensitivity for the diagnosis of MG [11, 12, 16].

In MuSK-MG, edrophonium may worsen patients' weakness, so if there is a clinical suspicion of MuSK-MG, the test is best not performed [16].

An alternative to edrophonium is neostigmine. This test is less accurate. However, it may be preferable to edrophonium in younger children who cannot cooperate fully [16].

Pharmacological tests are useful, especially in ocular myasthenia, but problems related to safety and drug availability have limited their use. In the USA, edrophonium has been discontinued since 2018. The Italian recommendations mention that neostigmine may be used as a third-line test in seronegative patients with normal electrodiagnostic results. According to the Guidelines of the Association of British Neurologists, the edrophonium test may be difficult to interpret [16].

Conditions that mimic MG may produce a positive result, and there are potential cardiac complications. Heat was noted to worsen MG fatigue and weakness, while cold improved them. The ice pack test consists of putting an ice pack over the eyes of a patient with ptosis. It was found to reduce ptosis and ophthalmoparesis. The test is used mostly for ocular MG. Some authors report sensitivities equal to that of single-fiber electromyography in patients presenting with ptosis and a very high negative predictive value. Specificity is about 25% [16].

The electrodiagnostic techniques in MG are a repetitive nerve stimulation study and single-fiber electromyography. Results of the repetitive nerve stimulation study are abnormal in approximately 75% of patients with generalized MG and in less than half with ocular MG. It is more likely to be abnormal in a proximal or facial muscle. It is also operator-dependent. Single-fiber electromyography reveals abnormal jitter in 95–99% of patients with MG if the appropriate muscles are examined [11, 12, 16].

The sensitivity of an anti-AChR antibody test is approximately 85% for generalized MG and 50% for ocular. Anti-AChR antibody concentrations vary widely among patients with similar degrees of weakness. Thus, antibody titers cannot predict the severity of disease in an individual patient. Early in the course of the disease, patients might be falsely negative. Patients with generalized MG who are anti-AChR negative should be tested for anti-MuSK antibodies. Striated muscle antibodies (titin, myosin, actin, and ryanodine receptors) are detected in 75–85% of patients with thymomatous MG. The presence of these antibodies in early-onset MG raises the suspicion of a thymoma. Every patient with confirmed MG should undergo a chest CT or MRI to exclude the presence of a thymoma [16].

Treatment

Anticholinesterase drugs comprise the first line of therapy. They cause temporary improvement of weakness, which passes when the short-term effect of the drug subsides. When the autoimmune nature of the disease was discovered, immunomodulatory treatments were introduced, starting with high-dose steroids, which can induce marked improvement and even remission [11, 13]. After high-dose steroids are introduced, there might be a temporary worsening of the weakness which might require cholinesterase inhibitors in milder cases or plasmapheresis in cases involving the respiratory muscles. In cases needing rapid response treatment, intravenous immunoglobulins can also be used with similar efficacy for plasma exchange, with fewer side effects [17].

Azathioprine, mycophenolate mofetil, cyclosporin, and tacrolimus are immunomodulatory drugs that affect lymphocytes through various mechanisms. They can be used as steroid-sparing agents when long-term treatment is needed [2, 11, 13, 18]. For refractory cases of MG, cyclophosphamide has been shown to induce remission for several years without relapse. Although these immunomodulatory drugs have been shown to be effective, they carry severe side effects, including increased tendency to infections and malignancies. Therefore, they should be used with consideration of future effects on the patient's quality of life. Another option for refractory cases is rituximab, a chimeric monoclonal antibody against the B-cell marker CD20 [19]. The presumed role of the thymus in MG has provided the justification for thymectomy as a treatment for non-thymomatous MG for nearly 70 years. Although no randomized trial has shown its efficiency, meta-analyses have shown that there is probably some benefit from the surgery. Early consideration of thymectomy should be considered in patients with AChR antibody-positive, generalized MG and in patients ages 18–50 years [2, 18]. Currently, other treatments are under evaluation, including B-cell depletion treatments (inebilizumab), an anti-CD-19 monoclonal antibody, complement inhibitors (eculizumab, zilucoplan), neonatal Fc receptor antagonists (Efgartigimod alfa), and hematopoietic stem cell transplantation [2, 18].

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Paraneoplastic Neurological Syndromes

81

Francesc Graus

Abstract

Paraneoplastic neurological syndromes (PNS) occur in patients with cancer typically before any other clinical suspicion of an underlying tumor. PNS are considered autoimmune disorders caused by an immunologic response against an antigen (onconeural antigen) expressed in the tumor and brain. This view is supported by the presence of autoantibodies against onconeural antigens in serum and CSF of patients with PNS. PNS are rare, with an incidence between 0.9 and 0.4 cases/100,000 people/year. The most common tumors are lung, mostly small cell lung carcinomas (SCLC), breast, and ovarian tumors, thymoma, and Hodgkin lymphoma. Prompt diagnosis is important to prevent the development of severe disability. The first diagnostic criteria for PNS were published in 2004, and the diagnosis was based on the presence of neurological syndromes that frequently associate with cancer (classical syndromes) or the presence of onconeural antibodies. In the 2021 revised criteria, a definite diagnosis of PNS can be accomplished when the patient presents a neurological syndrome with high risk (previously known as classical) or intermediate risk to associate with a tumor, neuronal antibodies with a high risk (>70%) (onconeural antibodies) or intermediate risk (30–70%) of cancer, and histological diagnosis of a tumor that is expected by the type of associated antibody or expresses the antigen recognized by the antibody. Although the 2021 diagnostic criteria do not capture all PNS, as they do not allow to diagnose as definite PNS neurologic syndromes without neuronal antibodies, the updated criteria represent a step forward to differentiate true PNS from neurologic syndromes that coincide in time with cancer diagnosis.

Keywords

Paraneoplastic neurologic syndromes · Onconeural antigens · Neuronal antibodies · Cancer

Paraneoplastic neurologic syndromes (PNS) are a group of neurologic disorders that may involve either the central or the peripheral nervous system and present with high frequency in patients with cancer that usually is not diagnosed at the time the PNS appears. Most PNS are considered autoimmune disorders characterized by an immunologic response against an antigen expressed in both tumor cells and neurons.

PNS are rare disorders, affecting less than 1% of all patients with cancer. The most common tumors are lung, mostly small cell lung carcinomas (SCLC), breast, and ovarian carcinoma, thymoma, and Hodgkin lymphoma. In epidemiological studies from regions of Italy, France, and the United States, the incidence of PNS ranges between 0.9 and 0.4 cases/100,000 people/year, with a tendency to increase in recent years, and a prevalence between 6 and 4 cases per 100,000 inhabitants. The increasing use of immune checkpoint inhibitors for the treatment of cancer has contributed to the rise of the incidence of PNS [1].

PNS are believed to be caused by the ectopic expression by tumor cells of antigens, called onconeural antigens, which are also present in the nervous system. The immune reaction mediated by antigen-specific T and B cells results in inflammatory infiltrates in the nervous system and tumoral tissue and the detection of neuronal antibodies in the serum and CSF. Some neuronal antibodies probably are not pathogenic as they recognize intracellular antigens and neuropathological studies support a T-cell-mediated neuronal damage. The subsequent description of antibodies against neuronal surface antigens, which are pathogenic, in patients with autoimmune encephalitis indicated that some of these antibodies associate with a high frequency (>50%) of tumors. In this scenario, the encephalitis must be considered a PNS in which antibodies, not T-cells, are pathogenic [2].

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General Clinical Manifestations

In PNS, the neurologic manifestations usually appear before the diagnosis of the tumor. The clinical syndrome develops in weeks or a few months and causes severe and irreversible neurologic impairment in many instances. Clinicians should include PNS in the differential diagnosis of subacute neurologic disorders not explained by other conditions, particularly in patients older than 50 years. An important clinical clue is that PNS may present with a multifocal disease involving distant and apparently unrelated areas of the nervous system. The suspicion of PNS must be high in those syndromes that are defined as "classical" or, according to the 2021 updated PNS criteria, high-risk for cancer because the association with cancer is high. Besides these "classical" syndromes, the recently updated 2021 criteria include a group of intermediate-risk syndromes in which the detection of neuronal antibodies is indicated to support a paraneoplastic origin (Table 81.1) [3]. Classical or high-risk neurological syndromes are described below, except Lambert-Eaton myasthenic syndrome (LEMS), which is described in another chapter of this book.

Table 81.1 Neurological syndromes included in the diagnostic criteria of PNS

High-risk neurological phenotypes
Encephalomyelitis
Limbic encephalitis
Subacute cerebellar degeneration
Opsoclonus-myoclonus
Sensory neuronopathy
Gastrointestinal pseudo-obstruction
Lambert-Eaton myasthenic syndrome
Intermediate-risk phenotypes
Non-limbic autoimmune encephalitis[a]
Brainstem encephalitis[a]
Morvan syndrome
Stiff-person syndrome[a]
Subacute myelitis
Sensorimotor polyradiculoneuropathies

[a] When associated with specific neuronal antibodies

Neuronal Antibodies

Several neuronal antibodies have been described associated with different PNS and particular tumors (Table 81.2). The neuronal antibodies have been classified in two groups. The first group includes those antibodies defined as high-risk for cancer (>70%) and those previously defined as onconeural antibodies. The specificity of these antibodies for the presence of PNS is very high, and only a few patients seropositive do not have cancer. The second group includes the neuronal antibodies with an intermediate risk (30–70%) for cancer and their detection is an indication for searching an

Table 81.2 Neuronal antibodies associated with PNS

Antibody	PNS	Associated cancer
High-risk for cancer (>70%) antibodies		
Hu (ANNA-1)	PEM, sensory neuronopathy, PCD, limbic encephalitis, gastrointestinal pseudo-obstruction	SCLC
CV2(CRMP5)	Similar to Hu plus chorea and sensorimotor polyradiculoneuropathies	SCLC, thymoma
SOX1	LEMS, PCD	SCLC
PCA-2	Similar to Hu	SCLC
Amphiphysin	Stiff-person syndrome, sensory neuronopathy, PEM	Breast, SCLC
Ri (ANNA-2)	Brainstem encephalitis, opsoclonus-myoclonus	Breast, SCLC
Yo (PCA-1)	PCD	Ovarian, breast
Ma2	Limbic/brainstem/diencephalic encephalitis, PCD	Testis, lung adenocarcinomas
KLHL11	Sensorineural hearing loss, brainstem encephalitis	Testis, germinoma
Tr (PCA-Tr)	PCD	Hodgkin lymphoma
Intermediate-risk (30–70%) for cancer antibodies		
P/Q type VGCC	LEMS, PCD	SCLC
NMDAR	NMDAR encephalitis	Ovarian teratoma (young females), adenocarcinomas (people >45 years)
AMPAR	Limbic encephalitis	SCLC, thymoma
GABAbR	Limbic encephalitis	SCLC
mGluR5	Encephalitis	Hodgkin lymphoma
CASPR2	Morvan syndrome	Thymoma

AMPAR α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, *ANNA* Antinuclear neuronal antibody, *CASPR2* contactin-associated protein-like 2, *CRMP5* collapsing response mediator protein-5, *GABAbR* gamma-aminobutyric acid b receptor, *KLHL11* Kelch-like protein 11, *LEMS* Lambert-Eaton myasthenic syndrome, *mGluR5* metabotropic glutamate receptor type 5, *NMDAR* N-methyl-D-aspartate receptor, *PCA* anti-Purkinje cell antibody, *PCD* paraneoplastic cerebellar degeneration, *PEM* paraneoplastic encephalomyelitis, *VGCC* voltage-gated calcium channel, *SCLC* small-cell lung cancer underlying tumor. Besides these antibodies, there are other neuronal antibodies that almost never associate with a PNS as, for example, leucine-rich, glioma-inactivated 1 (LGI1) antibodies that occurs in non-paraneoplastic limbic encephalitis [3].

High-Risk for Cancer Neurological Syndromes

Paraneoplastic Encephalomyelitis (PEM)

PEM is defined as the involvement of different areas of the nervous system over time. Two main syndromes are identified; the most common is typically associated with SCLC (in >80% of cases) and Hu (ANNA1) or less frequently CV2 (CRMP5) or amphiphysin antibodies. The most predominant clinical manifestations are sensory neuronopathy, followed by limbic encephalitis, brainstem/cerebellar symptoms, and dysautonomia [4]. The second syndrome associates with testicular tumors and Ma2 antibodies. The syndrome is characterized by a combination of limbic encephalitis and meso-diencephalic involvement causing hypersomnia, narcolepsy, gait instability, and supranuclear gaze paresis. Whereas the brain MRI is almost always normal in PEM with Hu antibodies, Ma2-associated PEM frequently shows temporal lobe and brainstem hyperintense lesions in FLAIR images that may enhance after gadolinium administration [5].

Limbic Encephalitis (LE)

LE is characterized by neurologic manifestations attributable to limbic (medial temporal lobe) structures, manifested as short-term memory loss, seizures, or psychiatric symptoms (depression, irritability, and personality changes). Onset is over days or weeks in more than 80% of cases. Mild (<50 lymphocytes/μl) CSF pleocytosis occurs in around 50% of cases and brain MRI show hyperintense FLAIR lesions in one or both medial aspects of the temporal lobes. The type of antibody positivity will indicate if the LE is paraneoplastic and the tumor search is indicated. Whereas the most frequent LE presents LGI1 antibodies, which do not associate with cancer, other antibodies conform three main subtypes of paraneoplastic LE: 1. Anti-Hu-associated LE predicts an underlying SCLC in up to 90% of cases. It may present isolated or multifocal disease, in 50% of cases, as a part of the spectrum of PEM [4]. 2. Anti-Ma2-associated LE: limbic involvement occurs in 80% of cases, with brainstem (73%) and diencephalic involvement (38%). The presence of anti-Ma2 antibodies is associated with testicular cancer in 90% of cases [5]. The syndrome is increasingly diagnosed in patients with lung cancer under treatment with immune checkpoint inhibitors [6]. 3. LE associated with antibodies against neuronal surface antigens. The antibody type usually predicts the underlying cancer. In patients with SCLC, the LE associated with gamma-aminobutyric acid b receptor (GABAbR) antibodies probably is more common than the LE associated with Hu antibodies. Patients with LE and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) antibodies frequently present lung cancer or thymomas, whereas those with mGluR5 antibodies associate with Hodgkin disease. The main feature of LE associated with antibodies against neuronal surface antigens is the usually good response to immunotherapy [7].

Paraneoplastic Cerebellar Degeneration (PCD)

PCD presents with a subacute history of weeks to months of truncal (wide-based gait) and appendicular ataxia (intention tremor) with or without dysarthria, nystagmus, vertigo, or diplopia. It usually stabilizes over 6 months but leaves the patient physically dependent in most cases. The pathological hallmark of PCD is the loss of Purkinje cells in the cerebellum. Several clinical-immunological associations have been identified:1. anti-Yo (PCA1) PCD accounts for up to 40% of cases of PCD and is one of the most homogeneous subgroups of PNS, affecting women with a median age of 60–65 years, 80% of them with gynecologic cancer (breast and ovary, usually localized and treatable). PCD appears before cancer in 61% of patients. Despite PCD is not the main cause of death, most patients remain neurologically impaired, with almost null neurologic recovery after oncologic or immunosuppressive therapy [8]. 2. PCD associated with SCLC accounts for 32% of all PCD, affecting equally men and women after 65 years of age and initially manifested as a subacute picture (few weeks to 1 month) of cerebellar dysfunction that may progress to a multifocal disease, evolving to PEM. Neural antibodies are present in up to 70% of patients; the most common are SOX1 and P/Q type voltage-gated calcium channel (VGCC) antibodies, which frequently occur together, followed by Hu antibodies [9]. Patients with PCD and P/Q type VGCC antibodies sometimes present clinical or electromyographic features of concomitant LEMS. The prognosis of PCD associated with SCLC is poor, with no neurological improvement to cancer therapy or immunosuppression. 3. Anti-Tr PCD represents 14% of all PCD. This type of PCD usually affects male patients with Hodgkin lymphoma. The clinical symptoms are confined to the cerebellum without involvement of other areas of the nervous system. The tumor is found in 90% of cases (almost always a Hodgkin lymphoma), with a mean time of 3.5 months, preceded by PCD in 80% of them. Anti-Tr autoantibodies may be present only in the CSF and, unlike other onconeural antibodies, may disappear after successful treatment of the tumor. Unlike other PCD types, up to 15% of patients improve after treatment of the Hodgkin lymphoma and immunotherapy. The better response to treatment is probably explained by the fact that the antigen recognized by Tr antibodies, Delta/Notch-like epidermal growth factor-related receptor (DNER), is expressed in the membrane of neurons, whereas the other onconeural antibodies recognize intracellular antigens [8].

Opsoclonus-Myoclonus Syndrome (OMS)

OMS is defined by the presence of opsoclonus (involuntary and irregular saccadic eye movements in all directions), usually associated with arrhythmic action-myoclonus involving the trunk, limbs, and head. Symptoms of cerebellar dysfunction are frequent, such as ataxia and dysarthria. Onset is usually subacute, and, after excluding other causes, two subgroups must be taken into account: paraneoplastic and idiopathic, both of them with a presumed autoimmune basis. The most frequent neoplasms are neuroblastoma in children and breast or SCLC in adults, lacking specific antibodies except in patients with breast cancer that associate with Ri (ANNA2) antibodies. CSF is normal or discloses mild pleocytosis, and MRI usually has no alterations [10].

Sensory Neuronopathy (SN)

The SN is caused by damage to sensory neurons in the dorsal root ganglia. SN is characterized by a subacute history (weeks) of pain and paresthesias with a multifocal and asymmetric pattern, invariably involving upper limbs during evolution. Lower limbs are also affected with variable intensity. The neurologic examination shows the abolition of the deep tendon reflexes and involvement of all modalities of sensation but with clear predominance of the joint position and vibratory senses. SN appears as an isolated manifestation in 24% of patients, being the predominant syndrome in 74% of anti-Hu-associated PEM. SN typically associates with clinical manifestations involving other areas of the nervous system. A relatively common involvement is the neurons in the myenteric plexuses that cause gastrointestinal pseudo-obstruction (persistent vomiting, constipation, and X-ray evidence of intestinal dilation). The typical SN has a subacute onset and progresses rapidly to involve the four limbs and then may stabilize although, by the time it does so (6–9 months), the patient may be confined to bed or chair due to ataxia. In 10% of the patients, the neuropathy runs a mild, very slowly clinical evolution. These patients may remain ambulatory and with an independent life for years in the absence of any antitumoral or immunosuppressive treatment. The CSF may show mild lymphocytic pleocytosis. EMG studies disclose abolished sensory nerve action potentials. Motor neurography is usually normal but may show evidence of mild denervation or slowed nerve conduction velocities. SCLC is diagnosed in 70–80% of cases with Hu antibodies. Other antibodies instead of Hu can be detected, such as CV2 (CRMP5) and amphiphysin. Oncologic treatment is the mainstay therapy of SN and the only independent predictor of stabilization or improvement [4].

Intermediate-Risk for Cancer Neurological Syndromes

Intermediate-risk for cancer neurological syndromes share as main characteristic that in some instances the probability of a paraneoplastic etiology is high and determination of neuronal antibodies is indicated (Table 81.1). In the cases of non-limbic autoimmune encephalitis [7] and stiff-person syndrome [11], the type of antibody associated will indicate if the syndrome can be paraneoplastic. For example, stiff-person syndrome commonly associates with glutamic acid decarboxylase (GAD) antibodies, but in the minority of patients, who have instead amphiphysin antibodies, the paraneoplastic risk is high, and many present an underlying SCLC or breast cancer. Patients with brainstem encephalitis myelitis and polyneuropathy should also be tested for neuronal antibodies after other, most common, etiologies are ruled out. Some clinical manifestations are important to raise the suspicion of a paraneoplastic etiology. Paraneoplastic brainstem encephalitis may present with predominant sleep disturbances (hypersomnia, narcolepsy) associated with Ma2 antibodies, sensorineural hearing loss and KLHL11 antibodies, OMS and Ri antibodies, or central hypoventilation and Hu antibodies [12]. Paraneoplastic myelitis frequently associates with symptoms of peripheral neuropathy, whereas paraneoplastic polyneuropathies frequently present with pain and an asymmetric distribution. Electromyographic studies show an axonal pattern and frequent involvement of the nerve roots. The most common antibodies in paraneoplastic myelitis or polyneuropathies are CV2 (CRMP5) followed by Hu and amphiphysin [13, 14].

Diagnostic Criteria

According to the recently updated criteria published in 2021, the diagnosis of PNS should be based on the neurological syndrome (Table 81.1), the type of neuronal antibody detected (Table 81.2), and the histological confirmation of cancer. Based on these three criteria, PNS are classified as "definite," "probable," "possible," or "non-PNS" according to the score obtained from the sum of the points which are

Table 81.3 Diagnostic criteria for paraneoplastic neurological syndromes (PNS)

		Points
Clinical level	High-risk phenotypes	3
	Intermediate-risk phenotypes	2
	Defined phenotype epidemiologically not associated with cancer	0
Laboratory level	High-risk antibody (>70% cancer association)	3
	Intermediate risk antibody (30–70%)	2
	Lower risk antibody (<30%) or negative	0
Cancer	Found, consistent with phenotype or antigen expression demonstrated	4
	Not found (or not consistent) but follow-up <2 years	1
	Not found and follow-up ≥2 years	0
Diagnostic level	Definite Probable Possible Non-PNS	≥ 8 6–7 4–5 3

allocated depending on the type of neurological syndrome, antibody, and cancer (Table 81.3). It is mandatory to exclude other possible causes for the neurologic symptoms before the diagnosis of PNS is established. A limitation of these new criteria is that neurologic syndromes without associated neuronal antibodies cannot achieve the level of definite PNS; the best example is OMS associated with neuroblastoma or SCLC that do not present neuronal antibodies [10]. In addition, neurologic syndromes with neuronal antibodies that rarely associate with cancer cannot be diagnosed of definite PNS even if the tumor expression of the neuronal antigen recognized by the antibody is demonstrated. An example is a patient with myelitis and aquaporin-4 antibodies in whom the diagnosed tumor expresses aquaporin-4 [15].

Management and Prognosis

The first step is to make an early diagnosis. This aim can be accomplished by knowledge of clinical clues to recognize PNS, determination of serum or CSF neuronal antibodies, and use of sensitive imaging techniques, such as positron emission tomography (PET) for tumor detection. However, even a negative PET does not rule out the presence of a microscopic tumor, and serial examinations with PET or CT scan are indicated in patients with high risk of a PNS [16]. The main objective in the management of a patient with a PNS is to cure the underlying cancer and to improve or stabilize (in those PNS associated with neuronal death) the neurological dysfunction. The positive effect of tumor treatment has been observed in several PNS, such as paraneoplastic opsoclonus-myoclonus, LEMS, and anti-Hu-associated PNS [17].

Several immunosuppressor therapies, including corticosteroids, plasmapheresis, rituximab, and IVIG, have been used in the treatment of PNS. The impact of these therapies is unclear because the number of patients treated are relatively low, patients also receive antineoplastic treatment, and randomized prospective studies are lacking. Although, theoretically, immunosuppression could exacerbate tumor growth, we did not find that these treatments were an adverse prognostic factor for survival. The effect of immunotherapy in PNS has to be considered according to the type of PNS and the associated antibody. In patients with limbic encephalitis associated with antibodies against surface receptors, LEMS, and the opsoclonus-myoclonus syndrome who have a functional, rather than an irreversible, neural damage, immunotherapy is effective. In PNS associated with onconeural antibodies that target intracellular antigens, there is a variable degree of irreversible neuronal damage, so the objective of any immunotherapy should be stabilization rather than improvement of the neurological symptoms [18–20].

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Guillain-Barre Syndrome and Other Immune-Mediated Neuropathies

82

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Abstract

Immune-mediated neuropathies are a heterogenic group of disorders caused by an autoimmune response and often associated with autoantibodies against various neuronal epitopes. The main pathophysiological mechanisms of nerve injury include immune-mediated demyelination, axonal damage, and vasculitic-induced nerve ischemia. Diagnosis is based primarily on the clinical presentation and course, together with electrophysiological studies, testing for autoantibodies, and, when needed, cerebrospinal fluid examination and nerve biopsy. Immune-mediated neuropathies frequently, though not universally, respond to immune therapies including corticosteroids, plasma exchange, and intravenous immunoglobulins.

Keywords

Immune-mediated neuropathies · Autoantibodies · Guillain-Barrésyndrome · CIDP · Multifocal motor neuropathy · Vasculitic neuropathy · Small fiber neuropathy

Immune-mediated neuropathies are a heterogenic group of disorders deemed to be caused by an autoimmune response against peripheral nerve antigens. They are often associated with autoantibodies to various neuronal epitopes and frequently, though not universally, respond to immune therapies, including corticosteroids, plasma exchange (PE), and intravenous immunoglobulins (IVIg). The major immune-mediated neuropathies and the associated autoantibodies are listed in Table 82.1. In this chapter, focus will be made on Guillian-Barre syndrome as the most widespread and studied pathology in this group. In comparison with it, other immune polyneuropathies, will be discussed.

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Table 82.1 List of the major immune-mediated neuropathies (abbreviations in parentheses) and the main associated autoantibodies

	Antibodies
Guillain-Barre syndrome (GBS)	
Acute inflammatory demyelinating polyneuropathy (AIDP)	Unknown. Possibly, GM2?
Acute motor axonal neuropathy (AMAN)	GM1, GM1b, GD1a,GalNac-GD1a, GQ1b
Acute motor sensory axonal neuropathy (AMSAN)	GM1, GM1b, GD1a
Miller Fisher's syndrome (MFS)	GQ1b, GT1a, GM2
Chronic inflammatory demyelinating polyneuropathy (CIDP)	Unknown
Multifocal motor neuropathy (MMN)	GM1
Paraneoplastic neuropathies	Hu, CV2
Vasculitic neuropathies	ANCA
Vasculitic neuropathy in primary vasculitis syndromes (e.g. PAN)	According to the main diagnosis
Vasculitic neuropathy in connective tissue disorders (e.g. RA)	According to the main diagnosis
"Nonsystemic" vasculitic neuropathy	Unknown
Neuropathies associated with monoclonal gammopathies	
Neuropathy in multiple myeloma	MAG, GM1
Neuropathy in MGUS	MAG, non-MAG monoclonal IgM, GM1, sulfatide Or chondroitin sulfate, disialosylated gangliosides (GD1b, GD3, GQ1b, and GT1b)
Neuropathy in other monoclonal gammopathies	MAG
Small fiber neuropathy	Unknown

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Guillain-Barre Syndrome: An Overview

Guillain-Barre syndrome (GBS) is an acute autoimmune peripheral neuropathy that may cause muscle weakness and sensory dysfunction and progresses over a period of several days and up to 4 weeks. The four most common subtypes of GBS are acute inflammatory demyelinating neuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor sensory axonal neuropathy (AMSAN) and the Miller Fisher's syndrome (MFS). The limb weakness is usually ascending, accompanied with the loss of deep tendon reflexes and, in some cases, also with the sensory deficit. In the case of MFS, facial muscles are also involved [1]. Less frequent clinical presentations include bilateral facial palsy with paraesthesia, paraparetic, pharyngeal–cervical–brachial variants, overlap of classic GBS with MFS, and Bickerstaff brainstem encephalitis [2].

GBS is considered to be the most common cause of acute generalized paralysis, which can lead to diaphragm paresis and severe autonomic dysfunction. If similar clinical manifestations are observed for weeks and months, usually, without leading to life-threatening conditions, chronic demyelinating polyneuropathy (CIDP) can be suspected. If a patient has an oncological or rheumatological disease, it is crucial to exclude polyneuropathies associated with such conditions (paraneuroplastic, monoclonal gammapathy, or vasculitis-assosiated). Single muscle paresis may be suspicious of multifocal motor neuropathy. In cases, where the neuropathic pain manifests after an infectious disease or silicone implantation, without paralysis or numbness, and with a negative result on electromyography, small fiber neuropathy may be suspected [3].

Epidemiology

GBS occurs throughout the world, affecting children and adults, with a median incidence of 1.3 cases/100,000 population (range, 0.4–4.0) and male predominance [1]. Mortality rates can be as high as 10% due to neurological deficits and autoimmune disorders. The four GBS subtypes differ in their worldwide incidence. In Western countries, demyelination accounts for almost 90% of all GBS cases, and in Asian countries, the majority represent axonal lesions [1], although recent data shows the number of axonal forms growing in Europe as well [4]. AIDP was evaluated in 60–80% of cases in North America and Europe, while axonal form was reported in 3–17% in Europe, in 23–65% in Asia, and 67% in Bangladesh [5]. Miller Fisher syndrome and Miller Fisher-Guillain-Barré overlap syndrome were more common in Asia ($n = 14/63$, 22%) than in the other two regions (Europe/Americas: $n = 64/562$, 11%; Bangladesh: $n = 1/107$, 1%). Regional differences in the infections' prevalence may be related to this phenomenon.

Etiology and Pathogenesis

There is considerable evidence supporting an immune-mediated mechanism in GBS, though the pathophysiology is different in the various subtypes. The most likely etiological factors are viral and bacterial infections, as well as severe physical stresses, e.g., operations or injuries. About two thirds of GBS patients reporting an infection within a 6-week period prior to the diagnosis, generally either a flu-like episode or gastroenteritis. The most frequently identifiable infections that are "classical" for GBS are *Campylobacter jejuni*, *Mycoplasma pneumoniae*, and such viruses as cytomegalovirus, Epstein-Barr, and hepatitis E virus.

Recently, a number of papers were describing new etiological factors of GBS. These pathogens include Zika virus, middle east respiratory syndrome coronavirus (MERS-CoV), and Sars-Cov-2 infections [2, 6]. In the recent systematic review, 99 cases of GBS complicating the course of COVID-19 were identified based on 79 selected articles [7]. Other authors, on the contrary, have not noted in their centers an increase in the incidence of immune neuropathies after a novel coronavirus infection and consider GBS to be a rare complication [6]. A considerably controversial issue appears to be the relationship between vaccination against SARS-COV-2 and the development of GBS. Several cases are described on average within 2 weeks after the introduction of the vaccine, especially after ChAdOx1-S vaccination [8] or influenza vaccine.

The pathophysiology of GBS is very complex and require extended future studies. Various mechanisms are considered by which infectious agents can cause immunological damage to the nervous tissue. The destruction of the hemato-encephalic or hemato-neural barrier may be crucial and the most probable pathological mechanism is the cross-reactivity between the infectious and human proteins. In AIDP, as well as in CIDP, the neuropathy is mainly demyelinating: macrophages invade the myelin sheaths and denude axons [1]. Axonal damage can occur secondarily when the inflammation is severe. T-cell reaction against aberrant myelin proteins is also possible [8]. The histological appearance of AIDP resembles experimental autoimmune neuritis, which is caused predominantly by T cells directed against peptides from the myelin proteins P0, P2, and PMP22 [9]. The exact role of T-cell-mediated immunity in AIDP remains unclear, and there is also some evidence for the involvement of antibodies and complement [9].

In the axonal subtypes, AMAN and AMSAN, the main pathology is axonal injury rather than demyelinative one, and the pathophysiology is better understood. Strong evidence now exists that these axonal subtypes are caused by autoantibodies to gangliosides on the axolemma. An interesting observation is that the lipo-oligosaccharide from the *Campylobacter jejuni* bacterial wall contains ganglioside-like structures, thus promoting an immune response in some patients by the mechanism of molecular mimicry [1, 9].

Nevertheless, the real-life pathological evidence appears to be more complex. Upon revising the initial pathological description of axonal GBS, it has been determined that active axonal degeneration and demyelination coexist in spinal roots, while peripheral nerve trunks primarily exhibit Wallerian-like degeneration. Based on nerve ultrasonographic features and autopsy studies, the ventral rami of spinal nerves are identified as a prominent site of involvement in early GBS. Thus, the primary process in GBS can take place in the ventral and dorsal branches of the spinal nerves, rather than in more distal rami. Indeed, the place where the spinal nerves leave the central nervous system and start to be covered with myelin has a more complex architecture and can be a site of aggression for the autoimmune process. Also, the development of immune edema can increase the pressure in the endoneural space, leading to the microcirculatory dysfunction and damage of the nervous tissue [4].

In addition to GBS and CIDP, small fiber neuropathy may also have possible infectious genesis, the pathogenesis of which also includes cross-reactivity, various antibodies to nervous tissue, and the role of the T cell and complement is also not excluded. Like GBS, neuropathy of small fibers in most cases is reversible and does not progress in a progressive or relapsing-remitting manner typical for "classical" autoimmune diseases [10].

Clinical Course

Paresthesias and slight numbness in the toes and fingers are the earliest symptoms. It is important to note that such patients usually do not have an acute outbreak of infection at the time of the development of autoimmune disorders; their viral load and other indicators are usually lower than the expected ones. The major clinical manifestation is weakness that evolves more or less symmetrically and reaches its nadir 2–4 weeks after onset of disease. The symptoms progress with an ascending pattern from the lower to the upper limbs in 56% of patients, involve the four limbs simultaneously in 32% of patients, and spread from the upper to the lower limbs in 12% of patients [1]. The proximal as well as distal muscles of the limbs are involved. Involvement of the facial muscles is frequent, whereas the ocular motor muscles are usually spared, except with MFS. The weakness of the respiratory muscles may be severe enough to require assisted artificial ventilation in about 25% of the patients. More than half of the patients complain of pain and an aching discomfort in the muscles, mainly those of the hips, thighs and back. After a variable plateau phase, recovery begins with return of proximal, followed by distal, strength over weeks or months. Between 4 and 15% of patients die, and up to 20% are disabled after a year despite modern treatment [9]. The classic sensorimotor form and acute inflammatory demyelinating polyneuropathy were found to be more commonly observed in the post-COVID condition, although there were also reported cases of rare variants such as MFS [2].

GBS appears to be a disease of the peripheral nervous system, but involvement of the central nervous system occurs in about 30% of cases. The symptoms can vary, spanning from mild neuropsychiatric issues such as depression and anxiety to more severe cases where individuals may remain in a deep unconsciousness. Other common signs include the presence of hypnagogic or hypnopompic vivid dreams, various types of illusions (such as visual, tactile, auditory, and illusions of body tilt), as well as visual and tactile hallucinations. Additionally, some individuals may also experience delusions, often of a paranoid nature [11].

Considering metabolic dysfunction, hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) should not be missed and not to be confused with IVIG-related pseudohyponatremia [11].

Autonomic involvement is common and may cause urine retention, ileus, sinus tachycardia, blood pressure variability, cardiac arrhythmia, postural tachycardia, hypotension, and posterior reversible encephalopathy syndrome (PRES) [11].

Diagnosis

Asbury and Cornblath's clinical criteria for the diagnosis of the GBS [12] are widely accepted and are listed in Table 82.2.

The most important laboratory aids to the clinical diagnosis are the electrophysiological studies and the CSF examination. The CSF is typically under normal pressure, contains an increased protein content, and is acellular or contains only

Table 82.2 Asbury and Cornblath's clinical criteria for Guillain-Barrésyndrome diagnosis

Features required for diagnosis
1. Progressive motor weakness of two or more limbs[a]
The degree ranges from minimal weakness of the legs, with or without mild ataxia, to total paralysis of the muscles of all four extremities and the trunk, bulbar and facial paralysis, and external ophthalmoplegia
2. Areflexia
Universal areflexia is the rule, though distal areflexia with definite hyporeflexia of the biceps and knee jerks will suffice if other features are consistent
Clinical features strongly supportive of the diagnosis(in order of importance)
1. Progression. Symptoms and signs of motor weakness develop rapidly but cease to progress by 4 weeks into the illness. Approximately 50% will reach the nadir by 2 weeks, 80% by 3 weeks, and more than 90% by 4 weeks
2. Relative symmetry
3. Mild sensory symptoms or signs
4. Cranial nerve involvement. Facial weakness occurs in approx. 50% and is frequently bilateral. Other cranial nerves may be involved (e.g., those innervating the tongue and muscles of deglutition, extraocular motor nerves). On occasion (less than 5%), the neuropathy may begin in the nerves to the extraocular muscles or other cranial nerves
5. Recovery. It usually begins 2–4 weeks after progression stops. May be delayed for months. Most patients recover functionally
6. Autonomic dysfunction. Tachycardia and other arrhythmias, postural hypotension, hypertension, and vasomotor symptoms, when present, support the diagnosis. These findings may fluctuate
7. Absence of fever at the onset of neuritic symptoms
Features casting doubt on the diagnosis
1. Marked, persistent asymmetry of weakness
2. Persistent bladder or bowel dysfunction
3. Bladder or bowel dysfunction at onset
4. More than 50 mononuclear leukocytes/mm^3 in CSF
5. Presence of polymorphonuclear leukocytes in CSF
6. Sharp sensory level
Features that rule out the diagnosis
1. A current history of volatile solvent abuse. This includes huffing of paint lacquer vapors or addictive glue sniffing
2. Abnormal porphyrin metabolism indicating a diagnosis of acute intermittent porphyria.
3. A history or finding of recent diphtheritic infection, either faucial or wound, with or without myocarditis
4. Features clinically consistent with lead neuropathy (upper limb weakness with prominent wrist drop; may be asymmetrical) and evidence of lead intoxication
5. The occurrence of a purely sensory syndrome
6. A definite diagnosis of a condition such as poliomyelitis, botulism, hysterical paralysis, or toxic neuropathy (e.g., from nitrofurantoin, dapsone, or organophosphates)

[a] Excluding Miller Fisher and other variant syndromes

a few lymphocytes (usually less than 10, rarely more than 50 mononuclear leukocytes/mm^3) [1]. The protein content in the CSF may not be raised until 10 days after onset of disease, and lumbar puncture may need to be repeated if the diagnosis remains doubtful.

Electrophysiological studies of both motor and sensory peripheral nerves play an important role in supporting the diagnosis and help differentiate between the main subtypes of GBS—i.e., between AIDP and AMAN or ASMAN. The particular electrophysiological abnormalities found in each subtype of GBS have been thoroughly described [9]. However, unlike the clinical diagnostic criteria, which have been agreed on, there is no consensus on electrophysiological criteria for classification. We direct readers to neurophysiological criteria proposed by Hughes and Cornblath for AIDP, AMAN, and AMSAN [9].

Up to half of GBS cases have specific autoantibodies. Several anti-ganglioside antibodies are associated both with AMAN (GM1, GM1b, GD1a, GQ1b, and GalNac-GD1a) and with AMSAN (GM1, GM1b, GD1a) but not with AIDP [1, 9]. The Miller Fisher's syndrome, characterized by a triad of ophthalmoplegia, ataxia, and areflexia, is associated with anti-GQ1b, a specific and sensitive anti-ganglioside antibody, present in more than 90% of the patients with MFS, BBE, pharyngeal-cervical-brachial variants and absent in other forms of inflammatory neuropathy [9]. GQ1b is highly expressed at the paranodes and the neuromuscular junctions of cranial nerves [13].

It is noteworthy that individuals with GBS could have serum antibodies that targeted a heterodimer complex of GD1a and GD1b gangliosides rather than targeting each ganglioside independently. The strength of antibody binding to a specific ganglioside could be either enhanced or reduced by the presence of other gangliosides in close proximity, as well as with the specific glycolipids' arrangement. This discovery may bring more light on immune neuropathy predisposition in different patients.

The combination of sensorimotor symptoms, facial palsy, respiratory insufficiency, and a demyelinating electrophysiological subtype has been observed in GBS patients with viral infections like CMV and Zika virus and, possibly, is associated with viral infections in general. In cases of bacterial infection, e.g., *C. jejuni*, a pure motor and axonal type of GBS are usually observed [7]. In the first few days, it may be difficult to determine the subtype of fiber lesion on ENMG due to immunologic edema of the nerves [4].

In the case of the rest of the immune-mediated neuropathies, a variety of other antibodies have been described, but they are not strictly pathognomonic for a specific disease. In CIDP, myelin proteins, such as protein 0 (P0), protein 2 (P2), peripheral myelin protein (PMP)-22, and connexin, are considered one of the putative targets [14]. Recent studies describe anti-CNTN1, anti-neurofascin 155, anti-neurofascin 186, and autoantibodies to Ranvier intercept proteins. The antibodies that target these axo-glial proteins are primarily (though not exclusively) of the IgG4 isotype. IgG4 antibodies do not activate the complement system, have a limited ability to bind to Fcγ receptors, and are generally considered to have anti-inflammatory properties that require further studies [8]. In multifocal motor neuropathy (MNN), IgM to the ganglioside GM1 are present in 40–60% of patients [15]. As ganglioside GM1 is most abundant in peripheral motor nerves, especially at the nodes of Ranvier and adjacent paranodes, disruption of these functions is assumed to lead to conduction disturbances and conduction block, a key feature of MNN. In the case of paraneoplastic neuropathies, most associated with non-small cell lung cancer, small cell lung cancer, and breast cancer, the debut of neurological symptoms can manifest earlier than the diagnosis of cancer. The Updated Diagnostic Criteria for Paraneoplastic Neurologic Syndromes distinguish a group of high-risk antibodies (>70% associated with cancer): Hu (ANNA-1), CV2/CRMP5, PCA-2/microtubule-associated protein, and amphiphysin, that can be used for cancer screening [16].

Treatment

IV immunoglobulins and plasmapheresis appear to be equally effective for the treatment of GBS but do not significantly reduce mortality. A combination of plasma exchange (PE) and IVIg do not seem to produce significant extra benefit [17]. Patients undergo five sessions of PE with 50 ml/kg plasma each session, administered over 1–2 weeks [18]. Approximately 10% of patients feel better immediately after this therapy, but then their condition deteriorates sharply, promising a poor prognosis. PE is not recommended for patients with severe dysregulation of autoimmunity, due to the possibility of the life-treating complications [18].

The standard treatment for GBS is one course of IVIg of 2 g/kg over 5 days or 0.4 g/kg daily for 5 days. IVIg has been found to be safer than PE, having a lower frequency of multiple complications. Thus, its efficacy, safety, and availability make IVIg the treatment of choice in many patients with GBS. Corticosteroids are not effective, with the possible exception of very early administration or if no other options are available [18]. It is noteworthy that corticosteroids are not as effective for motor neuropathy, whereas most patients respond to IVIg with marked rapid improvement in muscle weakness.

Several novel treatment options are currently being investigated. Given the data on the involvement of complement activation in the pathogenesis of GBS, the efficacy and safety of eculizumab, a humanized monoclonal recombinant antibody to complement factor 5, for severe forms of GBS, is being investigated [19]. The neonatal Fc receptor (FcRn) is responsible for regulating the concentration of endogenous IgG, thus helping maintain immune homeostasis. By inhibiting FcRn, the level of IgG in the body can be reduced, as seen in successful animal experiments. Another approach is to enhance the degradation of antibodies, which can be achieved through the use of immunoglobulin G-degrading enzymes and similar methods. Additionally, blocking the role of C5b-9 anti-C1q antibody (M1) may also be beneficial in certain cases [18].

Unlike GBS, in CIDP the standard protocol considers the prescription of steroids as useful. Intravenous or subcutaneous immunoglobulins and PE can also be applied, and approximately 50–70% of patients respond to this therapy. It is worth noting that a purely motor or multifocal CIDP responds better to IVIG and may even get worse when prescribed steroids. The recommended initial IVIg dose is 2 g/kg and requires not less than three courses. Notably, more frequent administration of the IVIG with lower doses and rare administration of the drug but with high doses apparently do not differ in effectiveness [8]. A PE course of 5–10 every-other-day sessions within 2–4 weeks is commonly used. More than half of the patients are improving, but then their condition may get significantly worse; therefore, a combination with other methods of treatment may be necessary. Among the novel treatment options, Rituximab may be discussed, especially for those patients who have IgG4 antibodies and respond poorly to IVIG [8].

In most cases of nonsystemic vasculitic neuropathies, long-term immunosuppressive therapy is required. A feature is the recommendation of dual therapy consisting of high-dose prednisone combined with glucocorticoid-sparing agents as a standard initial therapy. Azathioprine, methotrexate, cyclophosphamide, and rituximab can be used as a glucocorticoid-sparing agent, the choice depends on the symptom's severity, patient comorbidity, and side effect profile. IVIg may be beneficial in cases of resistant vasculitic neuropathy [20].

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Neuromyelitis Optica

83

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Abstract

Neuromyelitis optica (NMO), also known as Devic syndrome, is defined clinically by severe inflammatory lesions in the optic nerves and spinal cord. Though it was lumped with multiple sclerosis for many years, it is now a clearly defined disease entity by clinical, imaging, and laboratory criteria. The main laboratory markers are high levels of antibodies to aquaporin 4, which is localized in the most affected areas. This disease may be the first of many to be separated out of the group of multiple sclerosis syndromes.

Keywords

Neuromyelitis optica · Devic syndrome · Aquaporin 4 · Multiple sclerosis

Introduction

Neuromyelitis optica (NMO, Devic's syndrome) is a demyelinating disease of the central nervous system, characterized by optic neuritis and transverse myelitis. This syndrome has raised much debate for many years, the key question being whether it represents a variation in the multiple sclerosis (MS) spectrum or is a separate disease. The clinical data that supports NMO as a separate disease include the relatively specific involvement of the optic nerve and spinal cord by very severe clinical relapses which in many cases resolve only partially [1]. The debate over NMO has been very much resolved in recent years, and it is now clear that it represents a well-defined disease entity. The first major step forward was finding detectable serum antibodies that target the water channel aquaporin-4 (AQP4-IgG) [2, 3]. The specificity of AQP4-IgG facilitated an even greater expansion of the clinical spectrum of NMO, leading to the new term—NMO spectrum disorders (NMOSD)—that was introduced in 2007 [4]. Currently, NMOSD includes AQP4-antibody-seropositive autoimmune astrocytopathic disease, MOG-antibody-seropositive inflammatory demyelinating disease, and double-seronegative disease with distinct clinical manifestations [5]. To put it into plain words, NMOSD is an umbrella term that includes NMO itself as well as forms of NMO with similar clinical findings and negative AQP4-IgG tests, both its *formes frustes* and closely related syndromes [6].

Epidemiology

NMOSD has specific features of prevalence, sex-age ratio, and geographical distribution not only in comparison with MS but also when comparing subgroups of this spectrum. The highest incidence rates were observed in middle-aged adults (40–59 years), while MS is characterized by an earlier onset (from 28 to 31 years) [7]. AQP4-positive disease has

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the highest female-to-male ratio (up to 9:1); for MOG antibody, the gender ratio is closer to 1:1 [8]. Geographic prevalence varies markedly, which was earlier interpreted as specific variants of MS in certain ethnic groups. Prevalence is highest in the African population, up to 10/100,000 population, among East Asians ~3.5/100,000 population, while among Caucasians it reaches only ~1/100,000 population. NMOSD makes about 1–2% of all demyelinating diseases in the Western world and about 3% of patients report a family history of this disease. Genetic and clinical associations with other autoimmune diseases, especially with lupus and sarcoidosis, are also widely mentioned [9].

Etiology and Pathogenesis

NMOSD is an example of an autoimmune disease primarily mediated by the humoral immune system. Detection of specific target antibodies to aquaporin-4 was the finding that contributed to the differentiation of NMOSD from MS. AQP4 is a water channel protein in astrocyte processes involved in the formation of the blood-brain barrier, most abundant in the periaqueductal and periventricular regions, and the spinal cord gray matter [3]. AQP4-IgG autoantibodies due to the possible cross-reactive mechanisms play a direct pathogenic role in NMOSD, as demonstrated in studies with recombinant antibodies derived from patient sera after a first clinical attack that induced NMO-specific immunopathology in rats [10]. Antibody binding to the AQP4 receptor leads to the activation of the classic complement cascade and complement-dependent cytotoxicity to astrocytes [11]. Also, AQP4-positive astrocytes initiate production of IL-6 that impairs endothelial cell function, leading to disruption of the blood-brain barrier, increases chemokine production, and additional granulocyte infiltration [12]. So, the process of demyelination of NMOSD is suggested to be secondary to primary astrocytopathy.

Myelin oligodendrocyte glycoprotein (MOG) expressed on the surface of myelin sheath has been identified as a candidate for autoantibodies in inflammatory demyelinating diseases of the CNS [13]. Despite the fact that these antibodies were found in approximately 40% of AQP4-IgG-negative patients [14], nowadays, (MOG)-IgG-associated disease (MOGAD) is more and more considered as a separate entity by different authors, giving it specific diagnostic criteria.

Clinical Manifestation

Core clinical features include typical NMO, limited forms (optic neuritis and longitudinally extensive transverse myelitis lesions), and brainstem encephalitis [6]. Acute area postrema syndrome and diencephalic lesions should also be taken into consideration. All patients with one of these symptoms as well as with suspected encephalitis of unknown origin should undergo a profound neurological examination.

Optic neuritis can manifest with declined and blurred vision, retrobulbar pain, pupillary defect, papilledema, and/or color desaturation [6]. Brainstem encephalitis include multiple symptoms like nausea, vomiting, hiccups, headaches, sleep and cognitive impairment, seizures, and in rare cases—hypersomnolence/narcolepsy or a syndrome of inadequate antidiuretic hormone secretion (SIADH) [6]. Myelitis results in para/tetraplegia, respiratory failure, and tonic spasms with usually more than three vertebral segments spreading [9]. Pain is another important clinical sign and may be present in the forms of neuropathic complaints, tonic spasms, girdle-like dysesthesia, and hyperalgesia/allodynia [6]. Patients with young-onset NMOSD were more likely to have optic neuritis as an onset attack, while older-onset patients often developed myelitis as the initial presentation.

NMOSD is associated with other autoimmune diseases such as lupus erythematosus, Sjögren's disease, myasthenia gravis, and other connective tissue disorders [15], as well as genitourinary, breast, lung, gastrointestinal, and hematology cancer [16].

The course of the disease is usually relapsing but may be monophasic in AQP4-IgG negative patients [6]. However, the interval between attacks can vary significantly, so it is advisable to consider any case of the disease as relapsing. Respiratory insufficiency and urosepsis due to the neurological deficit are one of the most common causes of death in this group [6]. The expanded disability score (EDSS) and functional system scores (FSS) were adopted from MS to measure disability in NMO [17].

Diagnosis

The significant advances in diagnosing NMO and its variants offer a unique opportunity to develop specific and better therapies for this disease. Profound neurological examination, cranial and spinal MRI, and serum AQP4-IgG antibody testing are essential [6]. Lumbar punction and detailed ophthalmological examination, including MRI and confocal microscopy, may be also undertaken. The currently accepted clinical criteria for NMO are detailed in Table 83.1.

MRI Evidence

Patients may show normal cerebral MRI results. Nevertheless, optic nerve lesions and brainstem lesions that are corresponding with the clinical findings should be taken into consideration. It is especially possible to evaluate dorsal medulla oblongata/area postrema foci, hypothalamic/thalamic lesion, or periependymal brainstem lesion on brain MRI.

Laboratory Testing

According to the International Consensus Diagnostic Criteria, the spectrum of NMO is divided by AQP4-antibody serostatus (AQP4-antibody-serosepositive NMOSD/AQP4-antibody-seronegative NMOSD/NMOSD with unknown AQP4-IgG status). The study of the NMO IgG found that it is bound to the aquaporin-4, which is present at the astrocyte-endothelial junctions of the blood-brain barrier [6]. Decrease in the levels of aquaporin-4 is also a very early and significant stage in pathological NMO lesions, which are clearly differentiated by this measure from MS lesions in histopathological studies [7]. Oligoclonal IgG bands in the cerebrospinal fluid (CSF) are relatively uncommon in NMO relative to MS and may serve as additional laboratory criteria for the disease [8].

AQP4-IgG seropositive patients account for up to 80% of all patients with NMOSD [18]. The 2015 International Expert Panel diagnostic criteria for NMOSD included detection of AQP4-IgG. The recommended method is cell-based serum assays over indirect immunofluorescent assays and ELISA because of their lower sensitivity and higher false-positive rate [19]. Notably, serum testing is preferred as the sensitivity of detecting AQP4-IgG in the serum is higher than those in cerebrospinal fluid (CSF), so CSF should only be tested in seronegative patients.

Table 83.1 Diagnostic criteria for neuromyelitis optica NMO [4]

Definite (NMO) criteria require:
1. Optic neuritis
2. Myelitis
And at least two of three supportive criteria:
1. MRI evidence of a contiguous spinal cord lesion 3 or more segments, in length
2. Onset brain MRI nondiagnostic for multiple sclerosis
3. NMO-IgG seropositivity
CNS involvement beyond the optic nerves and spinal cord is compatible with NMO

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Other possible causes of neuromyelitis should be considered, especially, MOG-Ab-associated disease and, surely, MS. However, other autoimmune (sarcoidosis), infectious, para−/neoplastic (spinal cancer, lymphoma), genetic, and vascular diseases have to be taken into account.

Several red flags that require in-depth diagnosis should be considered. These include a rapidly progressive, aggressive course of the disease, its further progressive deterioration for more than 1 month, the absence of autoantibodies to aquaporin or the absence of their IgG fraction in the serum, positive results both of antibodies to aquaporin, and to MOG, seropositive results to herpes viruses. When performing a brain MRI, foci with gadolinium enhancement for more than 3 months or those, that are not responding to therapy should be alerted. Also, if the patient has other autoimmune diseases, oncology, or a chronic infection, a profound analysis should be performed [6].

Treatment

Basic therapy includes immunosuppressive and immunomodulatory drugs, such as prednisolone, azathioprine, and mycophenolate mofetil (Table 83.2). Monoclonal antibodies, targeted at B cells, IL-6, and C5 component of complement, such as eculizumab, satralizumab, inebilizumab (FDA approved), rituximab, and tocilizumab (non-FDA approved), are a promising tool to prevent relapses in such patients. In the meta-analysis by Aungsumart et al., these medications demonstrated over 80% significantly lower risk of relapse over the standard treatment [20]. Apheresis therapy prescrip-

Table 83.2 Neuromyelitis optica treatment options

NMOSD treatment options	
Acute attacks	
Intravenous methylprednisolone	1000 mg daily for 3–5 consecutive days
Plasma exchange	Every other day up to a total of seven exchanges
Long-term immunotherapy	
Eculizumab	900 mg IV weekly for the first four doses, followed by 1200 mg every 2 weeks
Inebilizumab	300 mg IV, followed 2 weeks later by a second 300 mg dose
Satralizumab	120 mg by subcutaneous injection at weeks 0, 2, and 4, followed by a maintenance dose of 120 mg every 4 weeks
Rituximab	1000 mg infused twice over a 2-week interval, followed by 1000 mg infusion every 6 months
Tocilizumab	8 mg/kg (maximum 800 mg) IV every 4 weeks
Azathioprine	2–3 mg/kg daily for at least 6–12 months
Mycophenolate mofetil	1000–2000 mg daily for at least 6–12 months

tion might be a helpful addition in the attack treatment, while the basic therapy includes, i.e., methylprednisolone 1000 mg per day for up to 5 days, followed by an oral steroid application (1 mg/kg/day OR 20–30 mg/day with subsequent dose reduction) [17]. After the very first attack, a long-term immunotherapy must be suggested to patient. Several medications are strictly forbidden for NMOSD, including interferon beta, natalizumab, fingolimod, alemtuzumab, and dimethyl fumarate, being known to trigger severe attacks [17].

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Central Nervous System Vasculitis

84

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Abstract

To date, CNS vasculitis (CNSV) may also be classified as primary (PCNSV) or secondary (SCNSV) to systemic diseases, based on the size of the vessels involved, by MRI findings, and by histopathology based on brain biopsy. The updated literature points to advancements in radiographic modalities (MRI, vessel wall MRI, angiography with digital subtraction) that further aid in the diagnosis of CNSV and the differentiation between CNSV and its mimickers. However, the newer modalities cannot distinguish between primary and secondary CNSV so extra-CNS systemic findings, and lab tests are required. Cerebrospinal fluid analysis and serologic tests have not yielded more specific results than in the past. MRI-guided biopsy is more specific than a blind biopsy for positive results. Treatment options are limited and include steroids and cyclophosphamide. Occasionally, rituximab, IVIG, and others may be beneficial. We discuss the updated medical literature of the different entities and emphasize the utilization of more than one modality to confirm the proper diagnosis.

Keywords

CNS vasculitis · Primary · Secondary · Autoimmune diseases · Systemic vasculitis · MRI · Radiologic diagnostics

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Introduction

Vasculitis is a potentially life-threatening disorder with increased mortality due to irreversible ischemia and infarction. Primary central nervous system vasculitis (PCNSV) is a rare disease and the estimated prevalence in North America is 2.4/1,000,000 person-years. The mean age ranges from 24 to 63 years old, and 48% are women [1–3]. Due to the rarity of the disease, it is difficult to appraise epidemiological data.

PCNSV (primary angiitis of the CNS [PACNS], isolated or idiopathic granulomatous angiitis of the CNS, primary intracranial or cerebral vasculitis) refers to the heterogeneous clinic-pathological disorders that share the histopathology of inflammation of blood vessels leading to an array of neurological manifestations related to ischemic injury or hemorrhage to the brain [1–3]. Traditionally, the diagnosis depends on three criteria: transmural vascular inflammation of the CNS, no evidence of systemic involvement, and exclusion of other causes of inflammation [3].

The main histopathological types are granulomatous, lymphocytic, and acute necrotizing [2, 3]. The diagnosis of SCNSV is based on evidence of systemic involvement other than the CNS with serological and biopsy findings. The systemic vasculitides (SCNSV) are classically divided by the size of the blood vessels involved [3–5]. We suggested in the past an additional classification of CNSV [1]. In this chapter, we discuss the updated clinical and radiographic manifestations of the different entities. We suggest that new MRI and angiography technologies, and histopathology based on MRI-guided brain biopsy may further aid in the establishment of the proper diagnosis.

Radiological Diagnostics

Cerebral angiography has been the gold standard for radiological diagnosis of CNSV. However, angiography lacks specificity. Hence, various advancements to the classic MRI or MRA can be more useful in distinguishing CNSV from its

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mimickers. MRI findings differ among the various types of CNSV (based on the size of vessel involved). These new modalities are discussed here [2, 3, 6, 7].

Neuroimaging

MRI findings are very sensitive but not specific. A normal MRI rules out CNSV. MRI findings were described in 40 studies. In PCNSV, MRI findings of cerebral infarct, hemorrhage, leptomeningeal, and gadolinium enhancement correlated by 97% with angiography and 96% with biopsies. Cerebral infarcts were the most common finding in biopsy and angiogram-positive patients [8]. Less frequently, hemorrhage was detected. Parenchymal and leptomeninges involvement were found on biopsies but much less in angiograms. Parenchymal gadolinium enhancement was common with meningeal involvement [3]. MRI abnormalities were more frequent with lymphocytic, followed by granulomatous and necrotizing pathology. Intracranial hemorrhage was more common in patients with the necrotizing subtype. Granulomatous subtype presented with leptomeninges and parenchymal involvement [3]. High-resolution contrast-enhanced MRI to assess the vessel wall was described in five studies and found to be very accurate and associated with angiogram-confirmed patients [3].

Of 159 biopsy-confirmed patients, 33% of cases were confirmed by angiography with digital subtraction (DSA), depicting in descending order, segmental narrowing (66%), vascular beading (25%), focal stenosis (2.5%), and occlusion (2.0%) [8]. In addition, collateral circulation or microaneurysms were described [7]. Similarly, in 29% of cases, MRA also showed classical findings [3]. There was a clear association between DSA and MRA findings [8]. In one review, in patients who underwent both a biopsy and angiogram, 47% had a positive biopsy for vasculitis but a normal angiogram. On the other hand, MRI was abnormal in 97% of cases, and contrast-induced gadolinium was recommended. A normal MRI ruled out PCNSV [2, 3].

Vessel wall MRI (VW-MRI) augments information about the pathology of medium- and large-sized arteries and hence has value in diagnosing PCNSV. Patients with atherosclerosis will have eccentric nonuniform vessel wall thickness, while patients with PCNSV will have uniform concentric wall thickness. In addition, this method can aid in differentiating between vasculitis and its mimicker reversible cerebral vasoconstriction syndrome (RCVS). The vessel wall in RCVS is typically non-enhancing, while in vasculitis an intense enhancement is seen. Utilization of VW-MRI increased the sensitivity for vasculitis to 90.5% [6, 8].

Clinical Manifestations

Clinical manifestations in primary CNS vasculitis may present as focal or diffuse. In a systemic review of 911 patients, the common manifestations by frequency included focal neurological signs (63%), headache (51%), and cognitive impairment (41%). The mode of onset is acute or subacute. The classic presentation is progressive and cumulative with multifocal neurologic dysfunction. However, many exceptions exist. Also, ataxia of the limbs or gait and focal cortical dysfunction, including aphasia and seizures, are reported frequently. Nonspecific visual complaints occur in 15% of patients. Occasionally, patients present with multiple sclerosis-like disease or disease restricted to one portion of the nervous system. To make the diagnosis even more difficult, no specific neurological symptom or sign is attributed to PCNSV vasculitis [2, 3].

Biopsy and angiography confirmed patients presenting with cognitive decline, seizures, and focal neurological signs were less frequent. Cerebrospinal fluid (CSF) abnormalities occurred in 75% of patients and MRI abnormalities in 97% of cases. DSA was more sensitive than angiography for correlation with biopsy-proven primary CNS vasculitis [3]. Often there is no clear overlap between radiological and biopsy findings. This may be due to the skin lesions characteristic of this type of vasculitis. Hence, it is highly recommended that the biopsy be MRI-guided in order to increase the diagnostic yield [7].

CSF Analysis

Newer classifications for CNSV now include abnormal CSF findings necessary for the diagnosis of primary vasculitis. In a meta-analysis of diagnostic tests for primary CNS vasculitis, 581 of 911 patients had a CSF analysis performed. Pathological results (WBC: > 4 cells/microL and/or protein: >450 mg%) were found in 75% of biopsy-proven and 65% of angiogram-proven cases and regardless of histology subtype in more than 50% of samples. Patients with spinal cord involvement had positive findings in the CSF in 80% of cases [3].

Biopsy Findings: Histology

Transmural inflammation is the most specific histopathological finding in primary CNS vasculitis. The three histological types that characterize PCNSV are lymphocytic (45%), granulomatous (34%), and necrotizing (18%) [2, 9]. The vascular inflammation is usually of a chronic granulomatous nature, with monocytes, histiocytes, lymphocytes, eosinophils, and plasma cells invading the walls of small arteries and veins, particularly in the leptomeninges. Larger vessels may be involved but are a minor portion of involved vessels [9].

The etiology and pathogenesis remain obscure. CD4+ T lymphocytes are identified in some cases. Necrotizing and non-necrotizing vasculitis occur in SLE, systemic sclerosis, rheumatoid arthritis, Sjogren's syndrome, mixed connective tissue disease, and Behcet's disease**.** In the necrotizing subtype, there is wall destruction and intracranial bleeding [1, 9, 10].

Often, no direct correlation can be confirmed between angiogram and biopsy results. This could be due to different vessel sizes indicating a different histopathology. Biopsy confirmed PCNSV usually involves small vessels while angiogram confirmed involves the large vessels. Another possibility is that the biopsy was not performed from the affected area, due to the segmental pathology of the disease [2]. Furthermore, a biopsy for suspected PCNSV revealed an alternative diagnosis in 37% of cases [8]. Lastly, the rate of biopsy complications is 4–8% and includes hemorrhage and abscess formation [11].

PCNSV is divided into small vessel disease characterized by seizures, dyskinesia, cognitive impairment, and medium/large size vessel involvement characterized by focal deficits [12] (Table 84.1).

Secondary CNS Vasculitis (SCNSV)

SCNSV encompasses systemic diseases where the CNS is involved. These are autoimmune diseases including the following: systemic vasculitis (ANCA-associated vasculitis-AAV including small vessels), medium-sized vessels (polyarteritis nodosum [PAN], Kawasaki disease) or large vessel vasculitis (giant cell arteritis-GCA), systemic lupus erythematosus (SLE), Sjogren's syndrome, systemic sclerosis, mixed connective tissue disease, rheumatoid arthritis, juvenile dermatomyositis, and Behcet's syndrome [10, 12]. Sarcoidosis patients also can develop CNS involvement [11]. Neurosarcoidosis may appear as a single manifestation of sarcoidosis and will exhibit contrast-enhanced vessel wall. SCNSV may also be due to infections or malignancy [12, 13].

CNS involvement in PAN is characterized by manifestations including stroke, cerebral hemorrhage, and seizures. In eosinophilic granulomatosis with polyangiitis (EGPA), patients develop confusion, seizures, cranial nerve involvement, and optic neuropathy. Patients with hypersensitivity vasculitis (leukocytoclastic vasculitis) may develop, in severe cases, seizures, encephalopathy, stroke, and cranial nerve involvement. These findings are occasionally present in patients with cryoglobulinemia types II and III [1].

Neuropsychiatric lupus (NPSLE), appearing in up to 50% of patients, entails 19 different clinical manifestations, most

Table 84.1 Characteristics of CNSV

Type of CNSV characteristics	Primary CNSV	Secondary CNSV	CNSV mimickers
		SLE, AAV, Behcet, sarcoidosis	Malignancy, infections, RCVS, ICAA
Clinical	Seizures, dyskinesia, cognitive decline, focal deficits	Seizures, cognitive decline, focal deficits	ICAA (ABRA[a] & CAA-RI[a]): Cognitive decline
MRI	Infarcts, hemorrhage, leptomeningeal parenchyma	SLE-high intensity signals	Specific by systemic disease
Biopsy	Transmural inflammation Granulomatous, necrotic, lymphocytic	Specific histology by systemic disease	Specific by systemic disease
Angio + DSA	Segmental narrowing, vascular beading, focal stenosis, occlusion		
Vessel wall involvement			
Small	Seizures, dyskinesia, cognitive deficit	SLE, AAV	ICAA ABRA[a] & CAA-RI[a]
Medium	Focal deficits	SLE, AAV	ICAA ABRA[a] & CAA-RI[a]
Large	Focal deficits	GCA	

[a] Subgroup of ICAA: *ICAA* inflammatory cerebral amyloid angiopathy, *ABRA* amyloid angiopathy Ab-related angiitis, *CAA-RI* cerebral amyloid angiopathy-related inflammation, *DSA* digital subtraction angiography, *SLE* systemic lupus erythematosus, *AAV* ANCA-associated vasculitis, *GCA* giant cell arteritis

of which arise in the CNS as opposed to the peripheral neurological system. The most common findings are headache, mood disorders, and cognitive impairment [14, 15]. Twenty antibodies (11 brain-specific and 9 systemic) were described in NPSLE patients. These include antibodies that target brain-specific antigens (neuronal, ganglioside, synaptosomes, glia, methyl-d-aspartate receptors, lymphocytotoxic) and systemic antigens (nuclear, cytoplasmic, phospholipid, and endothelial cells). Cognitive impairment, psychosis, and depression were associated with many antibodies. Elevated titers of anticardiolipin antibodies (aCL) were reported most often in patients with cognitive impairment, psychosis, depression, seizures, chorea, and migraine [16]. To date, no diagnostic antibody array exists to determine NPSLE and its manifestations. In practice, elevated titers of serum and CSF anti-ribosomal P antibodies are associated with psychosis and depression. Other novel serum CNS biomarkers include serum neopterin and elevated titers of anti-NR2A/2B antibodies that may distinguish patients with NPSLE as opposed to lupus patients without neuropsychiatric symptoms. A decrease in titers may indicate a response to therapy [17]. Conventional radiographic evaluation of NPSLE includes MRI and SPECT or PET. The MRI depicts increased white matter T2/FLAIR hyperintensities [12].

Novel radiographic imaging may be beneficial in making a diagnosis of NPSLE. They include magnetization transfer imaging (MTI), MR spectrography (with reduced N acetyl-choline [NAA] to creatinine ratio and also an increased choline to creatinine ratio), and functional MRI. Arterial spin labeling (ASL), a contrast-free MR perfusion technique, identifies changes in cerebral blood perfusion [17].

Laboratory Tests

There is no specific laboratory test for CNSV. Laboratory tests are utilized predominantly to exclude other types of CNS involvement, and they include erythrocyte sedimentation rate. For example, extremely elevated ESR is indicative of temporal arteritis.

Lumbar puncture for CSF analysis is abnormal in autopsy-documented cases. A mild lymphocytic pleocytosis and slightly elevated protein levels are most common, again being nonspecific. Furthermore, oligoclonal bands with an elevated IgG index, low glucose levels, and elevated leukocyte counts of several hundred have all been reported [17]. Elevated titers of anti-ribosomal P antibodies are present in NPSLE patients experiencing psychosis or depression. Antiphospholipid syndrome (APS) may cause similar clinical manifestations, usually focal and not diffuse, as in PCNSV [17].

PCNSV Mimickers

Other entities have been described that may mimic PCNSV. These include reversible cerebral vasoconstriction syndrome (RCVS), which is the most common, and inflammatory cerebral amyloid angiopathy (ICAA) that includes cerebral amyloid angiopathy-Aβ-related angiitis (ABRA), cerebral amyloid angiopathy-related inflammation (CAA-RI), as well as intravascular lymphoma (IVL) [11, 12]. RCVS causes multifocal vasospasm triggered by pregnancy, medications (sympathomimetics, serotonin reuptake inhibitors), or posterior reversible encephalopathy syndrome. RCVS has a different arterial imaging, termed sausage on a string or segmental dilatation, in contrast to PCNSV. ABRA is a spontaneous form of autoimmune disease characterized by the deposition of amyloid β peptide in the blood vessels causing parenchymal and leptomeninges inflammation [11]. CAA-RI, similar to ABRA, is an inflammatory reaction to Aβ protein deposits limited to the perivascular area (as opposed to intramural involvement in PCNSV) [11, 12]. The commonalities and differences of CNSV are summarized in Table 84.1.

Approach to Diagnosis

A general consensus for the diagnosis of CNSV is reported in the medical literature. Recognition of the neurological entities and excluding other diseases is of the utmost importance because therapy will differ. Undiagnosed and untreated, the outcome of vasculitis is fatal. Absolute proof by tissue diagnosis has been a prerequisite in the past. However, recently due to advances in radiology, in some cases, CNSV can be diagnosed without the need for a brain biopsy. However, if a biopsy is necessary, a radiographic-guided technique is necessary so that the site of the biopsy will be accurately identified [3].

A careful history and physical examination are mandatory. The CSF in CNSV includes pleocytosis of >5 cells/mm^3, protein elevation greater than 100 mg/dl, evidence of intrathecal synthesis of immunoglobulin, and oligoclonal bands. Molecular, genetic, immunoassay, and direct staining techniques to exclude spirochetal, fungal, mycobacterial, and viral infections as well as examination of the CSF for possible malignant cells should be performed. Appropriate serological testing is recommended in the context of the clinical manifestations to differentiate between primary and secondary CNSV (i.e., ANA, ANCA, etc.) [17].

Other conditions mimicking CNSV are atrial myxoma, cholesterol emboli, infectious endocarditis, Sneddon's syndrome, antiphospholipid syndrome, encephalitis, neoplastic angioendotheliosis, malignant hypertension, and eclampsia.

Due to skip lesions found in CNS vasculitis, advanced radiology techniques as mentioned above are crucial in assessing CNS vasculitis or its mimickers. In addition, these methods will simplify taking biopsy specimens and avoid false-negative results [3].

Treatment

In a systematic review, there were no randomized trials on the appropriate therapy for PCNSV. The most common treatment was high dose glucocorticoids and oral or intravenous cyclophosphamide [1, 3, 9, 11]. Intravenous immunoglobulin (IVIG) therapy was beneficial for SLE patients with diffuse neuropsychiatric manifestations [18]. Rituximab is a possible option although only utilized in a few cases [11, 19]. In addition, mycophenolate mofetil and azathioprine can be used for maintenance therapy [11]. The limitation to the evaluation of the beneficial and safety potential of different therapeutics is the rarity of disease and, possibly, the difficulty of diagnosis [20].

Prognosis

CNSV is a progressive disease with an increased relapse and mortality rate. The prognosis of PCNSV is influenced by the severity of disease, older age at diagnosis, the presence of strokes, and relapses (more often with small vessel disease) [11]. In two large studies, with a follow-up of 19–57 months, patient mortality was as high as 23% and 30% for the patients who experienced a relapse [3].

The Dilemma

The medical literature is controversial on which diagnostic test is superior—the biopsy or radiographic findings. The biopsy exam revealed many false-negative results, while the angiogram revealed false-positive results [7]. Perhaps, with the advancement of techniques for MRI/MRA, radiographic criteria should carry a larger weight than the biopsy for diagnosis. Both remain necessary, however, due to the differential diagnosis and vasculitis mimickers.

Conclusions

The updated literature points to advancements in radiographic modalities: MRI, high resolution contrast enhanced MRI, MRI with SPECT/PET, MRA, and angiography with digital subtraction. These radiographic modalities enable us to differentiate between CNSV (primary and secondary) and its mimickers. CSF analysis and serologic tests have not yielded more specific results than in the past. MRI-guided biopsy is more specific than a blind biopsy. Additional investigation is warranted for other therapies such as rituximab, IVIG, and others. Furthermore, due to the severity of the disease and the potential utilization of immunosuppressive agents as the modality of therapy, it is imperative to assure a proper diagnosis.

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Autoimmune Chorea

85

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Abstract

Chorea (*χορός, dance*) is a movement disorder characterized by involuntary arrhythmic movement of a forcible, rapid, jerky type that may be simple or quite complex. The differential diagnosis of chorea is wide and finding the specific cause can be a challenging task. Autoimmune chorea can result from various immunological mechanisms. Sydenham chorea (SC) is a classic example, but other immune-mediated causes could be a reasonable causative alternative. This chapter reviews the autoimmune causes of chorea, defining diagnostic criteria based on the clinical presentation, serological, and neuroimaging markers.

Keywords

Sydenham chorea · Autoimmune chorea · Chorea gravidarum · Acute rheumatic fever · Autoantibodies · Autoimmune movement disorders

Etiology

SC (St. Vitus dance, St. Johannis chorea, chorea minor, rheumatic chorea) is the most common cause of chorea in childhood and one of the major clinical manifestations of acute rheumatic fever (ARF) occurring in 15–26% of patients after group A streptococcal (GAS) infections. The average age of presentation is considered to be between 5 and 15 y.o. with a peak age of 8–9 y.o. and female predominance [1]. The incidence of SC has decreased dramatically since the antibiotic era has started. However, the developing countries are still experiencing an increased risk of ARF and SC [2]. Occasionally, outbreaks of ARF occur even in developed countries [3].

For the adult-onset chorea, GAS infections are not the most common etiological factor. The only exception is chorea gravidarum (estrogen-induced chorea) as pregnancy-related variant, that is supposed to be associated with hormonal fluctuations, both caused by the natural course of the pregnancy and due to prescribed medications [1].Up to 75% of these women have a history of childhood SC, and the first trimester is the most susceptible starting period [4]. However, other causes of adult-onset chorea should be also excluded in pregnant women (Table 85.1).

Ischemic and hemorrhagic brain infarcts, nonketotic hyperglycemia, hereditary causes, autoimmune diseases, and paraneoplastic syndromes are usually more prevalent in adults. A review published by O'Toole and colleagues describes the frequency of different causes of adult-onset autoimmune chorea from 1997 to 2012 at Mayo Clinic (Rochester, MN) [5]. A total of 36 cases were identified. The majority of patients were female (58%), and the median age at symptom onset was 67 years. The paraneoplastic chorea group included 14 patients, and 22 patients were considered to be idiopathic. In the latter group, 19 of the 22 patients had a coexisting autoimmune disorder (e.g., systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS). No patient had a history of rheumatic fever or significantly increased antistreptolysin-O antibody titers.

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Table 85.1 Diseases characterized by chorea

Inherited disorders	
	Huntington disease
	Benign hereditary chorea
	Neuroacanthocytosis
	Dentatorubropallidoluysian atrophy
	Wilson disease
Rheumatic chorea	
Sydenham chorea	
Chorea gravidarum	
Drug-induced chorea	
	Neuroleptic
	Oral contraceptive
	Phenytoin
	L-dopa and dopamine agonist
	Cocaine
Chorea and systemic diseases	
	Systemic lupus erythematosus
	Antiphospholipid syndrome
	Thyrotoxicosis
	AIDS
	Paraneoplastic
	Polycythemia vera
	Stroke

Movement disorders are seen in less than 5% of patients with SLE and have a strong association with antiphospholipid antibodies in these patients. Based on the findings of the Euro-Phospholipid study, which examined a group of 1000 APS patients, chorea was found to be present in 1.3% of cases [6]. A strong association between chorea gravidarum and estrogen replacement therapy was evaluated, suggesting an important role of female hormones in the dopamine regulation. Multiple sclerosis is another classical autoimmune disease in which chorea can occur both as a result of the brain lesions and, probably, indirectly via systemic inflammation effects [7].

More and more evidence is accumulating about the role of viral infection and vaccination in the development of autoimmune chorea or hemichorea. The most probable triggers include HIV (and AIDS), herpes viruses, papillomavirus, and SARS-COV-2. Isolated cases of hemichorea are evaluated in elderly patients approximately a month after vaccination with Pfizer-BioNTech, ChAdOx1 nCoV-19 AstraZeneca vaccines, as well as HPV vaccines [7]. In the majority of cases, postvaccination chorea had a sudden onset within 2 weeks after the procedure. In a systematic review by Brandao and coauthors, chorea accounted for 1.1% of all COVID-associated movement disorders, with myoclonus and tremor predominating among the hyperkinetic dysfunction [8].

In rarer cases described in isolated observations, chorea has complicated various autoimmune encephalitis, such as anti-N-methyl-D-aspartate (NMDA) receptor encephalitis [9]. A new neurological entity, anti-IgLON5 disease, was observed in 2014, where movement disorders, including chorea, were accompanied by sleep disturbance and neurocognitive dysfunction [10]. There are anecdotal reports that describe cases of chorea associated with small-cell lung carcinoma, non–small-cell lung carcinoma, and hematologic malignancies with anti-Hu and anti-CRMP5 antibodies [5, 11].

Pathophysiology

SC is strongly associated with group A streptococcal infection. This condition is thought to be a result of the phenomenon called molecular mimicry, where the cross-reactivity between antiviral or antibacterial autoantibodies with the host antigen occurs. Antibodies against N-acetyl-b-D-glucosamine (NABG), a carbohydrate antigen of group A streptococci, are considered to lead to the different clinical manifestation of the ARF. These antibodies bind to lysoganglioside on the neuronal cell surface and/or interact with the intercellular motor protein β-tubulin and dopamine D1 and D2 receptors (D1R, D2R) [12]. Activated antibodies against basal ganglia cause a diffuse inflammatory process in the corpus striatum, mainly in the caudate nucleus. Symptoms of SC are believed to be caused by an imbalance between the dopamine system, the interstitial cholinergic system, and the gamma-aminobutyric acid (GABA) inhibitory system [1]. This cortical-basal ganglia-thalamocortical circuit disruption results in motor, behavioral, and cognitive symptoms and is supported by multiple neuropathological studies [13].

Clinical Manifestation

Classically chorea appears in several weeks after streptococcal pharyngitis and is often associated with hypotonia, emotional lability, and regression in school performance. The chorea typically starts with hand movement dysfunction and leads to generalized involvement of the face and feet; 20% of patients remain with hemichorea. Other motor symptoms include instability, ballismus, hypometric saccades, dysarthria, and hypotonia. Hypotonia can be severe, and the most pronounced form of SC is also known as chorea paralytica. Facial grimacing may be seen, as well as tics, especially vocal ones [1].

Psychiatric symptoms range from emotional lability to obsessive-compulsive disorder, attention deficit hyperactivity disorder (ADHD), and executive dysfunction. Up to 46% of children exhibit psychiatric symptoms. Behavioral change usually occurs during the first 2 months of ARF and generally wanes with the regression of motor symptoms; less frequently, they may persist for a longer time [14].

As behavioral complications are common in patients with rheumatic fever and chorea, CS is being considered as a model for pediatric autoimmune neuropsychiatric disorders. This concept has been called Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (PANDAS), which includes explosive onset of tics, obsessive-compulsive behavior, and other neuropsychiatric dysfunctions [15]. Although this concept has received heightened attention, to date it still remains controversial. Clear diagnostic criteria and strong evidence of therapeutic and psychiatric interventions are lacking.

Chorea can be the only symptom of the rheumatic disease, but clinical carditis (28%), echocardiography carditis (63%), and arthritis (17%) are frequently present.

SC is a self-limited condition; the improvement is gradual with a mean duration of 3–6 months; sometimes it takes more than 2 years. The treatment is applicable for severe cases with significant motor impairment.

Diagnostics

SC has a very specific clinical pattern, and all young patients with chorea-like movement, which decrease during sleep, need a detailed neurologic and cardiac examination (Table 85.2). Sore throat and the anamnesis of recent streptococcal infection may contribute to the diagnosis. Complete blood count, inflammatory markers, B12 level evaluation, liver and thyroid function test, as well as drug examination must be performed among the first ones.

Throat cultures are usually negative; however, it may be useful in recognizing recurrent GAS infections. The proof for streptococcal infection depends on the presence of specific antibodies. A rise in antistreptolysin O (ASLO) titer is seen in 80% of cases, with peak levels detected 4–5 weeks after the acute pharyngeal infection and weeks or months before the presentation of chorea. Anti-DNAse B is more sensitive marker and is elevated for a longer time; in one study [16], it was found positive in 98% of patients. Notably, the false-positive rate is high due to the high prevalence of GAS infections and the long duration of elevated antibody levels. Therefore, serial tests to detect an increase in antibody titer are recommended for a more accurate diagnosis of recent infection.

Table 85.2 Diagnostic criteria for Sydenham chorea

1. Chorea	
2. Evidence of streptococcal infection:	
	(a) ASLO titer
	(b) Anti-DNAse B
3. Carditis	
	(a) Auscultation findings
	(b) Electrocardiography
	(c) Echocardiography
4. Exclusion of other possible etiologies	
	(a) Serum copper
	(b) Ceruloplasmin
	(c) ANA
	(d) Anti-IgLON5 antibodies
	(e) IgG anti-GluN1 antibodies (anti-NMDA receptor encephalitis)
	(f) Anti-Hu, anti-CRMP5 (cancer-associated antibodies)
	(g) Family history (Huntington disease)

Neuroimaging (CT and MRI) scans typically are normal, although there may be an occasional reversible hyperintensity mainly in the basal ganglia [1] with the possible involvement of the caudate nucleus, putamen, thalamus, and cortex [7]. It is noteworthy that old lesions in these areas are sometimes described as incidental findings in the absence of chorea clinical signs. A recent relatively large study showed that swelling of the caudate nucleus was observed in only 30% of patients. In another study significant differences were observed only when comparing putamen volumes of patients and the control group [17].

A study of cerebrospinal fluid should be performed to assess pleocytosis, concentration of protein, glucose, and viral PCR, antinuclear antibodies, antiphospholipid and anticardiolipin antibodies, rheumatoid factor, onconeuronal autoantibodies (anti-NMDAR, anti-AMPA1 receptor, anti-AMPA2 receptor, anti-LGI1, anti-CASPR2, anti-GABArb receptor), as well as oligoclonal bands, as a sign of a dysimmune process [7]. The most common autoantibodies in paraneoplastic chorea are CRMP-5 (CV2) and ANNA-1 (Hu), ANNA-2(Ri), and PDE-10A IgG [18], where various oncological processes, including small-cell lung carcinoma, thymoma, non-Hodgkin's lymphoma, and tonsillar squamous cell carcinoma, should be approached. IgLON5 disease should be excluded, especially in elderly patients with parasomnia. Other promising autoantibodies for the idiopathic autoimmune chorea include GAD-65, voltage-gated calcium channel antibody (VGCC), and striational antibodies [18]; anti-basal ganglia antibodies have been found in 100% of patients with acute SC, but their role remains to be questionable.

Only in 23% of patients with SC, carditis is detected clinically or by auscultation. Echocardiography helps to detect silent valvular disease in additional 40% of patients.

Treatment

SC typically improves gradually, with symptoms lasting up to 15 weeks, full recovery occurs in almost every patient [19], and there is still no generally accepted treatment consensus. Primary etiological treatment is directed at the eradication of GAS infection, followed by secondary prevention of AFR relapse and progression of rheumatic heart disease.

The use of intramuscular penicillin G benzathine or amoxicillin is a preferable treatment. Secondary prophylaxis should be performed up to the age of 21 or up to 10 years after the disease as recommended by the WHO.

Large controlled trials on symptomatic treatment are lacking. The low-dose D2 blocking agents (haloperidol, pimozide, risperidone) and anticonvulsants (levetiracetam, valproic acid, carbamazepine) are the most recommended first-line therapy [19].

In moderate to severe cases, the use of immunomodulatory therapy is a possible beneficial option. The majority of studies have focused on the use of steroids, in particular oral prednisone and deflazacort, and intravenous methylprednisolone. All studies are limited to small samples, but steroid use appears to be effective in all cases [19]. There are anecdotical reports of the successful use of plasma exchange and IVIg [20]. Patients with APS and lupus respond to a variety of medications, including steroids, haloperidol, antiaggregants, anticoagulants, or combinations of therapy, and, of course, to oral contraceptive discontinuation if this was the cause. Antiplatelet and anticoagulant therapy may be beneficial for the further regression of neurological complications.

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Autoimmune Sensorineural Hearing Loss

86

Aharon Kessel and Elias Toubi

Abstract

Autoimmune sensorineural hearing loss (ASNHL) is typically presented by a bilateral rapidly progressive hearing loss that may also occur suddenly. Both autoantibodies and autoreactive T cells have been implicated in the etiopathogenesis of ASNHL. However, the identity of a specific or highly relevant inner ear self-antigen is still required. A definite diagnosis of ASNHL is usually made by excluding ototoxicity and other factors that mimic ASNHL but most importantly by demonstrating a good therapeutic response to corticosteroid treatment.

In this chapter, we will summarize many of the current studies that have established the idea of ASNHL being autoimmune in many cases. Also, we will address the need for specific diagnostic tools to better classify/diagnose this entity. These tools may lead to the development and application of immunosuppressive therapies to prevent the deterioration of hearing loss and could possibly prevent the requirement for cochlear implantation.

Keywords

Hearing loss · Autoimmunity · Antiphospholipid antibodies

Introduction

Sudden or progressive sensorineural hearing loss (SSNHL/PSNHL) is a pathology characterized by the sudden onset or progressive (over several months and sometimes days/weeks) of auditory impairment. It is considered idiopathic in most cases but may have genetic or acquired factors, such as viral infections, vascular diseases, ototoxic drugs, and autoimmune diseases.

The possibility that part of the previously considered idiopathic SSNHL or PSNHL were autoimmune in origin was first noted by Lehnhardt in 1958. He reported a patient, in whom progressive hearing loss became bilateral when an auditory deficit occurred in one ear in the past. He suggested that degeneration of inner ear tissues in one ear led to the production of anti-cochlear antibodies that eventually damaged the second ear. This assumption challenged the theory of the inner ear being an immunologically privileged site due to a blood–labyrinthine barrier.

Further support for this assumption was derived from a seminal study by McCabe in 1979, in which immunosuppressive therapy with corticosteroids and cyclophosphamide improved PSNHL rapidly. He and others believed that autoimmune SNHL (ASNHL) is mediated by inner-ear-specific autoreactive T cells. However, other studies provided evidence for a humoral (autoantibody)-mediated response against inner ear antigens.

The recognition of autoimmunity in patients with SSNHL and PSNHL was supported by the following:

(a) Sera of these patients contain reactive autoantibodies against different inner ear proteins, such as those of 28, 42, and 68 kDa.
(b) Disease-related autoantibodies such as the following: anti-dsDNA, antithyroid (ATA), anti-cardiolipin antibodies (aCL), and rheumatoid factor (RF) were detected in sera of these patients.
(c) Many trials have shown that prompt administration of corticosteroids and/or methotrexate double the likelihood of hearing recovery.
(d) Inner ear damage has been developed in animal models after immunization with heterologous cochlear antigens and immune adjuvant.

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(e) Inner ear pathology was documented to be part of the SLE-like phenomena, known to develop spontaneously in the MRL-lpr/lpr mice.
(f) Increased infiltration of both CD4þ and CD8þ T cells was observed in patients who were highly suspected to have ASNHL.

Sudden SNHL and PSNHL were also described as a result of microthrombosis and in association with anticardiolipin antibodies, suggesting that this organ-specific defect could be a presenting symptom of a primary antiphospholipid syndrome. In this chapter, we will summarize the data related to the autoimmune origin of PSNHL and SSNHL and discuss the need for a standardized evaluation of such patients, such as the creation of some diagnostic criteria that could improve the ability to decide when and how to treat these patients.

T-Cell-Mediated Autoimmunity in SNHL

A role for autoreactive T cells in the pathogenesis of PSNHL was reported two decades ago. The authors reported on leukocyte migration inhibition (LMI) in response to inner ear membrane in activated PBMC from 54 patients in whom ASNHL was suggested. The LMI assay used to be acceptable for measuring the ability of activated antigen-specific T cells to prevent macrophage migration in vitro. This assay is not used currently, but at the time it was in use, it indicated that T-cell responses to inner ear antigens should be considered when the pathogenesis of SNHL is studied.

In another previous study, the investigators implicated T-cell autoreactivity in ASNHL by demonstrating that PBMCs from these patients developed proliferative responses when incubated with human inner ear homogenate. In this study, it was shown that PBMC from 13 of 58 (22%) patients with unilateral or bilateral SNHL responded to human inner ear antigens. In comparison, PBMC proliferation to the same antigens was demonstrated in only 1 of 15 (7%) normal control subjects.

Later, the flow cytometer assay was used to analyze intracellular cytokine levels in peripheral blood from 19 patients with PSNHL and in 26 patients with Meniere's disease (MD), compared with that obtained from age and gender-matched healthy volunteers. The patients with PSNHL showed significantly increased levels of Th1 subsets (interferon-gamma-producing T cells) when compared with those in normal controls. The patients with MD showed significantly increased natural killer (NK) cell activity but no Th1 dominance. These results were further proofs for the role of T-cells and NK cells in the development of ASNHL.

In accordance with the above, it was shown by ELISPOT analysis that compared with normal hearing age- and sex-matched control subjects, ASNHL patients have significantly higher frequencies of circulating T cells producing either IFN-gamma ($p = 0.0001$) or IL-5 ($p = 0.03$) in response to recombinant human cochlin. In some patients, cochlin responsiveness involved both CD4þ and CD8þ T cells, whereas other patients showed cochlin responsiveness confined to CD8þ T cells. In this regard, the efficacy of tumor necrosis factor-alpha blockade in treating patients with ASNHL was shown by demonstrating the arrest of hearing loss, pointing to the beneficial effect of targeting cellular immunity in patients with ASNHL [1].

The inner ear-specific proteins cochlin and beta-tectorin were shown to be capable of targeting experimental autoimmune hearing loss in mice [2]. Five weeks after immunization of SWXJ mice with either Coch 131–150 or beta-tectorin 71–90, auditory brainstem responses showed significant hearing loss at all frequencies tested.

Flow cytometry analysis showed that each peptide selectively activated CD4þ T cells with a proinflammatory Th1-like phenotype. The adoptive transfer of peptide-activated CD4þ T cells into naïve SWXJ mice was followed by a significant hearing loss, providing a confirmation that ASNHL is a T-cell-mediated organ-specific autoimmune disorder. The expression of Fas ligand (FasL) in some nonlymphoid tissue, as in the anterior chamber of the eye, has been hypothesized to play a role in protecting the sensitive organs from activated T cells. Bodmer et al. [3] showed that under resting conditions, cochlear cells express little or no FasL. However, FasL was upregulated in adult cochlear cells after induction of a sterile labyrinthitis in vivo. The induction of FasL by inflammation may serve to limit cochlear immune responses and protect sensorineural tissue from immune and autoimmune damage. Thus, defects in FasL expression could facilitate the induction of autoreactive T-cell response and the development of ASNHL.

A summary of T-cell-mediated autoimmunity is shown in Fig. 86.1.

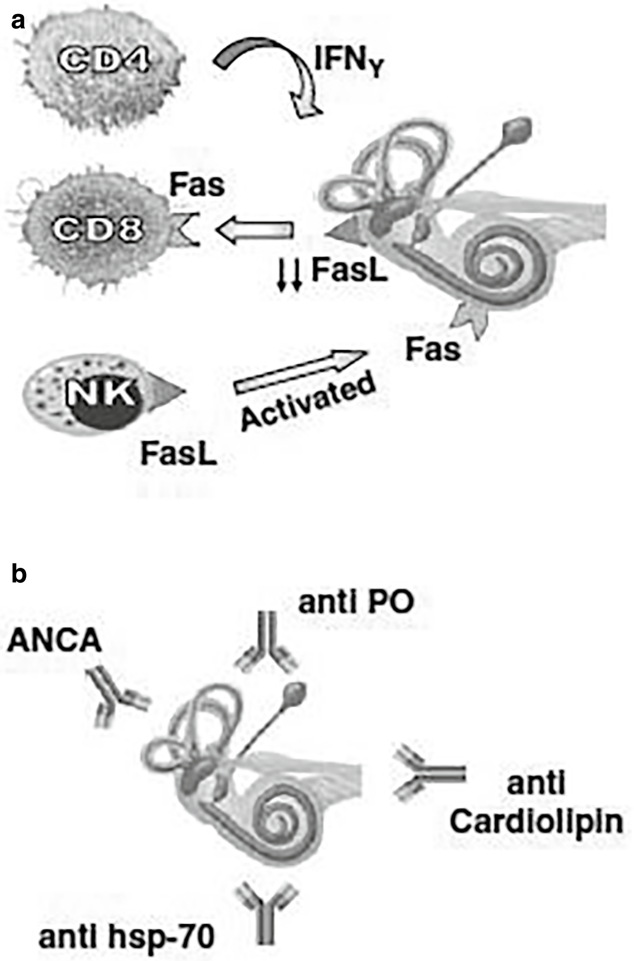

Fig. 86.1 (**a**) Cochlear tissues are attacked by autoreactive T cells: overproduction of IFN-gamabyCD4þ, the cytotoxic activity of CD8þ cells due to the attenuation of Fas-L expression on cochlear membranes, and the inability of eliminating T-cell invasion into inner ear tissues. NK cell activity via the Fas-FasL pathway. (**b**) The wide range of autoreactive antibodies against inner ear antigens and also cross-reacting autoantibodies against other self-antigens

Humoral (Autoantibody) Response in SNHL

Various nonspecific autoantibodies, such as antinuclear antibodies (ANAs), antineutrophil cytoplasmic antibodies (ANCAs), and anti-endothelial antibodies (AEAs), were widely reported in patients with ASNHL. These antibodies were suggested to function as cross-reacting antibodies that could possibly recognize inner ear proteins. However, looking into the autoantigens' origin in ASNHL, many specific antigens were proposed to play a role in this organ-specific autoimmune disease (Table 86.1).

The inner ear (namely, the endolymphatic hydrops) was already shown in earlier studies to contain several inner ear antigens, against which specific IgG was frequently found in the sera of both SSNHL and PSNHL patients [4].

In a further attempt to identify the main target antigens for autoantibodies reactive against guinea pig inner ear proteins, sera from 110 patients with a clinical diagnosis of either PSNHL (*n* = 32), MD (*n* = 41), SSNHL (*n* = 6), or other etiologies of hearing loss (*n* = 11) were screened by Western blot technique [5]. Forty-four percent of the patients' sera had antibodies to several inner ear proteins, of which the 30, 42, and 68 kDa proteins were found the most reactive. These proteins were demonstrated to be the major peripheral myelin protein PO and the beta-actin protein, respectively, while sequence analysis indicated that the 68-kDa protein was novel.

Furthermore, the presence of IgG antibodies against PO antigens in patients affected by sudden hearing loss and MD was evaluated in a most recent study [6]. Specifically, the PO positive band was detectable in 5 of 45 patients with unilateral auditory impairment and in 5 of 5 of those with bilateral forms. Among MD patients, the PO-positive band was detectable only in those with bilateral audio-vestibular impairment (*n* = 10). The positive reactions to PO in all bilateral sudden deafness patients found in this study strongly

Table 86.1 Summary of relevant autoantibodies in ASNHL

Non-specific autoantibodies			
Autoantibody	Target	Association	Reference
ANA	Nucleus	Bilateral SNHL	[4, 5]
ANCA	Neutrophils	Progressive SNHL	[19]
Anti cardiolipin	Phospholipids	Sudden SNHL	[17, 18, 20]
Specific autoantibodies			
Antigens	Specificity	Association	Reference
30–42 kDa	Inner-ear proteins	Bilateral SNHL	[12]
PO antigens and beta-actine	Inner-ear proteins	Progressive SNHL	[13]
68 kDa	Heat-shock protein	Steroid-responsive SNHL	[14, 15]

indicate that these pathologies are the result of an ongoing autoimmune process directed against specific antigens of the inner ear.

Harris and Sharp were the first to use Western blot analysis of serum from patients with bilateral PSNHL to report on the presence of nonspecific autoantibody directed against a 68-kDa (heat-shock protein-70) inner ear antigen [7]. The role of these antibodies in the development of ASNHL was repeatedly shown by others. Mathews et al. [8] presented a series of patients with clinically suspected autoimmune hearing loss in whom the presence of antibodies against bovine heat shock protein 70 (one of the many cross-reacting proteins against the inner ear in these patients) was a marker for the response to steroid treatment.

Aiming to identify whether the evaluation of anti-hsp70 antibodies is an accurate diagnostic tool in patients affected by ASNHL, a most recent prospective study was designed in which all patients with a consistent suspicion of ASNHL, anti-hsp70 antibodies were determined [9].

Anti-hsp70 antibodies were isolated in 52% of the study group patients and in only 4% of the control group ($p < 0.01$). This study confirms the value of the anti-hsp70 test in the serological diagnosis of autoimmune hearing loss and suggests that this is the only available diagnostic marker that identifies an autoimmune origin of hearing loss.

SNHL and the Antiphospholipid Syndrome (APS)

As in cutaneous and retinal manifestations of APS, it has long been suggested that a disturbed microcirculation caused by thrombosis is responsible for the development of SHNL. Measurement of the levels of anti-cardiolipin (aCL) antibody, lupus anticoagulant, and anti-b2 GP1 is performed in order to establish the diagnosis of APS in the appropriate clinical setting.

The syndrome and its manifestations can be primary (no other autoimmune disease coexist) or secondary (systemic lupus erythematosus being the most common associated autoimmune disease). In 1997, we reported our results on the presence of aCL in the sera of patients with SNHL [10].

Low to moderate positive aCL to one or both IgG/IgM isotypes were found in 8 of 30 (27%) patients, whereas none was detected in the healthy controls. In 1998, Heller et al. [11] studied the incidence and clinical relevance of antibodies to phospholipids in patients with sudden deafness ($n = 55$) and progressive inner ear hearing loss ($n = 80$). Antiphospholipid antibodies were demonstrated in 49% of the patients with sudden hearing loss and 50% of the patients with progressive hearing loss.

Both of these studies, though they reported the association between SNHL and the existence of aCL, did not investigate their persistency over time. Whereas autoimmune aCL is of persistent character and mostly seen in conjunction with anti-b2 glycoprotein-I antibodies (anti-b2 GP1), transient aCL, in the absence of anti b2 GP1, was reported to be the result of viral infections.

Recently, we assessed 51 patients who met the diagnostic criteria of SNHL in an extended study. We found low to moderately positive titers of aCL in 16 patients (31%) compared with two (6%) in the healthy controls. Six patients (12%, all aCL positive) were also positive for anti-b2 GP1. Three months later, positive aCL persisted in 7 (14%) patients, four of whom were also positive for anti-b2 GP1. This was consistent with the knowledge that anti-b2 GP1 antibodies are more specifically associated with thromboembolism, thus considering some cases of SNHL to be part of primary APS [12].

In another recent study, Mouadeb et al. investigated the possible association between antiphospholipid antibodies and SNHL of unknown origin in a cohort of 168 patients [13]. Forty-two patients (25%) had at least one elevated antiphospholipid antibody marker. Twenty patients had two or more positive test results. Of the 42 patients, 64% ($n = 27$) met the diagnostic criteria for MD, and the remainder were diagnosed with idiopathic SNHL. Within this group of patients, 24 (57%) had unilateral hearing loss, and 18 (44%) had bilateral hearing loss. These data further support the hypothesis that antiphospholipid antibodies are involved in the pathogenesis of some forms of inner ear dysfunction, presumably by causing microthrombosis in the labyrinthine vasculature.

In later studies, the finding of sudden SNHL was assessed among 13,250 patients with autoimmune diseases. Of these, 145 experienced an SSNHL event, which was significantly higher than in the control group and mainly observed among patients suffering from rheumatoid arthritis, multiple sclerosis, and APS [14]. In patients suffering from systemic lupus erythematosus and APS, the prevalence of bilateral SNHL was significantly high. Most patients with SSNHL and APS suffered also from vertigo and tinnitus. The auditory prognosis was poor with total hearing loss recovery reaching only 22% of patients [15].

Antiphospholipid antibodies may activate endothelial cells within the cochlear circulation, directly or by inducing the formation of free radicals that cause damage to the endothelium. These upregulated endothelial cells would initiate local microthrombus formation and subsequent ischemia to the inner ear. In these cases, treatment is directed toward preventing thromboembolic events. Of these medications, only warfarin has been shown to be beneficial in achieving antithrombotic effects. However, it is also accepted that steroid therapy, in addition to its anti-inflammatory effect, may also protect neural tissues from ischemic injury, stabilize the vascular endothelium, and restore the blood–brain barrier to normal. Although anticoagulant therapy was reported to be useful in some patients with SSNHL, it cannot become a routine regimen in the absence of histological or imaging tools to demonstrate microthrombosis in the inner ear of patients with SNHL. Thus, future studies should establish clear standard approaches regarding the need to start with anticoagulation therapy in patients who were admitted with SSNHL or PSNHL.

The wide range of autoantibodies in patients with ASNHL is summarized in Fig. 86.1b.

Treatment of ASNHL

Many trials have shown that prompt administration of corticosteroids can double the likelihood of recovery of hearing loss, especially when the pathology is strongly suspected to be of autoimmune origin. In this regard, Loveman et al. [16] analyzed the disease progression and treatment outcome of ASNHL by retrospective chart review of 30 patients. All subjects were tested for anti-68 kDa antibody, had audiometric evidence of hearing loss, and were treated with glucocorticoids. Ninety percent of subjects tested positive for anti-68 kDa antibodies. By audiometric testing, 50% of subjects were steroid responsive; minimal improvement or no change was recorded in 12%, and worsening occurred in 39% after steroid therapy. The three anti-68 kDa antibody-negative subjects were steroid unresponsive, and one progressed to complete deafness. The authors concluded that this series of patients with ASNHL suggests a more variable and benign course with a better prognosis than that previously reported.

In accordance with the above, it was shown that the antibody to 68-kDa protein was significantly associated with hearing improvement after corticosteroid therapy [17]. Patients whose serum was positive for the presence of these antibodies were nearly three times more likely to experience improved hearing with corticosteroid treatment than those who were serum-negative. Thus, antibodies to inner ear supporting cell antigens may have value in the diagnosis and treatment of patients with ASNHL.

Recent studies focused on more advanced therapeutic regimens for treating special cases of ASNHL. Therapeutic cochlear microperfusion, performed within the first 24 h of developing severe hearing loss, immediately restored on average 24 dB ($p < 0.007$) of hearing. This suggests that cochlear microperfusion is a promising new technique for treating severe deafness caused by inflammation.

In an early study, the intratympanic administration of tumor necrosis factor-alpha blocker—infliximab—to patients with ASNHL was tested. Intratympanic administration of infliximab was performed weekly for 4 weeks allowing steroids and methotrexate to be tapered off and resulting in hearing improvement and reduced disease relapse [18]. In a later study, long-term treatment with infliximab resulted in a sustained improvement of hearing function and tinnitus. However, its safety in long-term treatment should be further assessed [19]. The beneficial effects of IL-1 antagonist (anakinra) and rituximab (anti-CD20) were evaluated in immune-mediated inner ear disease. However, in a few studies, these drugs were found to achieve hearing improvement in more than 70% of treated patients [20].

Criteria for the Diagnosis of ASNHL

A definite diagnosis of ASNHL is possible when the following is available:

1. Progressive bilateral hearing loss occurs together with other symptoms of autoimmune diseases such as arthritis and skin vasculitis.
2. The presence of one or more autoantibodies, such as anti-hsp-70 antibodies, antinuclear, antineutrophil cytoplasmic antibodies, anti-endothelial cell, and anticardiolipin antibodies.
3. The prompt response to immunosuppressive (corticosteroids/ cytotoxic) therapy.

A probable diagnosis of ASNHL could be suggested when two of the above is available.

Concluding Comments

A better understanding of the autoimmune character of SNHL, and the need for specific diagnostic assays, may lead to better application of immunosuppressive therapies for preventing the progression of hearing loss, which may be profound and require cochlear implantation. The establishment of worldwide accepted criteria for the definite diagnosis of this entity could provide us with the tools to define the prevalence of ASNHL.

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Autoimmune Encephalitis

87

Mar Guasp and Josep Dalmau

Abstract

Autoimmune encephalitides (AE) associated with antibodies against neural (neuronal or glial) surface antigens yields a new category of diseases for which there is compelling evidence that the antibodies have direct pathogenic effects. Antibody-mediated AE occurs in persons of all ages, with some types affecting predominantly children and young adults. The diversity of clinical manifestations varies according to the type of autoantibody. The most common types are the encephalitis associated with NMDAR antibodies (which mainly affects children and young women, ~40% of the latter associated with ovarian teratoma), acute disseminated encephalomyelitis (ADEM, the most frequent in children, with white matter involvement and MOG antibodies in ~60% of cases), and limbic encephalitis, particularly a subtype that associates with LGI1 antibodies and predominantly occurs in patients older than 50 years). AE can be suspected on clinical grounds. However, in most instances, the definitive diagnosis requires the detection of neural antibodies in the cerebrospinal fluid (CSF), with the exception of MOG antibodies in ADEM, which are predominantly detected in serum. The importance of recognizing these clinical-immunological associations is that they inform about treatment, potential comorbidities (e.g., tumors), and prognosis. Despite the severity of symptoms, prompt diagnosis and treatment lead to improvement or good recovery in most cases.

Keywords

Encephalitis · Autoimmune · Cell-surface antigens · Neuronal antibodies · Glial antibodies

Autoimmune encephalitides (AE) constitutes an extensive and heterogeneous group of inflammatory central nervous system (CNS) diseases that are characterized by prominent neuropsychiatric symptoms and occur as a result of a brain-specific immune response, frequently in association with autoantibodies directed against neural (neuronal or glial) antigens [1]. They can be classified according to the mechanisms of disease, the type of antigen, and the presence or absence of an underlying tumor [2]. Regarding the association with a tumor, the detection of a neoplasm frequently serves to categorize the encephalitis as paraneoplastic, in accordance with recently updated 2021 criteria of paraneoplastic neurological syndromes [3] (PNS, discussed in another chapter of this book). Concerning the type of antigen, the most useful classification is based on its molecular identity and location, as intracellular vs cell surface (Table 87.1). The distinction between these two groups of disorders is important because some of the triggers and syndromes are similar but their pathogenic mechanisms and outcomes are different [1]. In the AE mediated by antibodies against neural surface antigens (referred to as antibody-

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Table 87.1 Comparison between disorders associated with antibodies against intracellular (previously named "onconeuronal") antigens and disorders with antibodies against neural cell-surface/synaptic antigens

Clinical syndromes associated with intracellular antigens	Clinical syndromes associated with cell-surface/synaptic antigens
Patients usually older than 50 years old	Patients of all ages; some antibodies preferentially occur in specific age groups
Multiple clinical syndromes	Frequently associated with encephalitis
Frequently paraneoplastic, except for GAD65 and other less common antibodies (e.g. AK5)	Variably paraneoplastic (0–70%), depending on the type of antibody (see PNS chapter)
Tumors almost always malignant (usually SCLC, breast and ovarian cancer, testicular seminomas, and Hodgkin lymphoma)	Tumors can be benign (e.g. ovarian teratoma or thymoma), or malignant
Monophasic neurologic disease	Relapses in ~10–35% of cases, depending on antibody
Outcome dependent on tumor control	Outcome not totally dependent on tumor control
Limited response to immunotherapy and poor prognosis	Good response to immunotherapy and better prognosis; 70–80% substantial recovery
Antibodies not pathogenic; equally present in serum and CSF. Syndromes probably are T-cell mediated	Antibodies are pathogenic; mostly present in CSF, less frequently in serum

mediated AE), antibodies typically bind to extracellular epitopes of cell-surface or synaptic proteins, ion channels, or receptors, reversibly alter the structure and function of the target antigens, and affect synaptic plasticity without causing major neuronal degeneration, which may explain the better outcomes [4]. The main triggers or factors that influence the development of AE include systemic tumors, viral encephalitis (mainly herpes simplex type 1), [5] novel cancer immunotherapies (such as immune checkpoint inhibitors), [6] and HLA susceptibility [7]. Nonetheless, most AE occur in patients with no apparent immunologic triggers.

Up to 12.6 per 100,000 persons are affected by encephalitis annually [8]. Of these, it has been estimated that 40–50% are caused by infectious agents (usually viral), 20–30% by autoimmune mechanisms, and the etiology of the rest is unknown. However, given the progressive discovery of autoantibodies, the growing awareness of these disorders, and the availability of specific diagnostic tests and clinical guidelines, the estimated incidence of AE is rapidly increasing, and it is currently similar to that of viral encephalitis in high-income countries. In particular, although the exact frequency of AE is unknown, studies in the United Kingdom, the Netherlands, the United States, and Spain suggest that antibody-mediated AE are as frequent as herpes simplex encephalitis [9]. Nowadays, there are 20 antibody-mediated neurological syndromes in which the associated antibodies and the corresponding syndromes have been defined. The most relevant are summarized in Table 87.2.

General Clinical Manifestations

AE can present with a broad spectrum of multifaceted syndromes and have a wide age and sex distribution that depend on the disorder. Some autoantibodies result in predictable and highly distinct syndromes (and have been used to name the new disease), whereas others associate with broader or less recognizable manifestations that may show substantial clinical overlap with each other [10]. The most common well-characterized clinical syndromes in AE are summarized below.

Most of these disorders manifest as subacute or rapidly progressive encephalitis syndromes, in which symptoms generally progress over a period of days or weeks. Approximately 60% of patients have prodromal low-grade fever, malaise, or headache, with initial findings that resemble those of cases due to viral infection. Although less frequently, up to 30% of patients do not present with the constellation of symptoms shown in Table 87.3 but develop a cerebellar syndrome or a chronic encephalopathy, resembling sometimes a neurodegenerative disease.

Common clinical features include a change in behavior, psychosis, seizures, sleep dysfunction (insomnia or hypersomnia), memory and cognitive deficits, abnormal movements, dysautonomia, and a decreased level of consciousness, with or without other focal neurological deficits. However, they typically do not carry systemic manifestations other than autonomic dysfunction, which makes this group of diseases separable from systemic autoimmune disorders that may affect the CNS, such as systemic lupus erythematosus.

As mentioned, AE can occur with or without cancer. The frequency of associated tumors, which can also be benign, ranges from 0% to 70% depending on the disorder, and within a specific disorder, it may vary according to the age and sex of the patient [3].

Anti-NMDAR Encephalitis

The encephalitis characterized by antibodies against the N-methyl-D-aspartate receptor (anti-NMDAR) is the most

Table 87.2 Most common neural (neuronal and glial) surface antibodies associated with AE

Antibody	Main syndrome	Main presenting symptoms	Median age (range); M:F ratio	MRI brain findings[a] (% of patients)	Frequency of tumor and type	Recommended sample for antibody testing
NMDAR	Anti-NMDAR encephalitis	Children: seizures, abnormal movements. Adults: behavioral changes, psychiatric symptoms	21 years (2 months–85 years); 1:4	Normal findings (70) or transient nonspecific changes	Varies with age and sex; ovarian teratoma in 40–50% women aged 18–45 years	CSF; serum negative in 15%
LGI1	Limbic encephalitis	Seizures (i.e., FBDS), hyponatremia, short-term memory loss	64 years (31–84); 2:1	Increased signal in medial temporal lobes (80)	<5% thymoma	CSF; present only in serum in a few patients
MOG	ADEM, cortical encephalitis with seizures	Confusion, decreased level of consciousness, seizures, cerebral monofocal and polyfocal CNS deficits, optic neuritis, transverse myelitis	10 years (2–40); 1:1	Tumefactive, large, bilateral, ill-defined brain lesions, often with deep grey matter, brainstem and cerebellar involvement. Unilateral or bilateral cortical leptomeningeal enhancement	No cancer association	Serum; present only in CSF in a few patients
AMPAR	Limbic encephalitis	Confusion, memory loss; in rare cases, psychiatric symptoms	56 years (23–81); 1:2.3	Increased signal in medial temporal lobes (70)	60% lung (SCLC), thymoma, breast cancer	CSF
GABA$_A$R	Encephalitis with frequent refractory seizures, status epilepticus	Seizures, confusion, behavioral changes	40 years (2 months–88 years); 1:1	Cortical and subcortical lesions involving two or more brain regions (80)	30% thymoma	CSF
GABA$_B$R	Limbic encephalitis with early and prominent seizures	Seizures, memory loss, confusion	61 years (16–77); 1.5:1	Increased signal in medial temporal lobes (45)	50% SCLC	CSF
CASPR2	Limbic encephalitis, Morvan syndrome, neuromyotonia	Memory loss, insomnia, dysautonomia, peripheral-nerve hyperexcitability, neuropathic pain, ataxia	66 years (25–77); 9:1	Increased signal in medial temporal lobes (65)	<5% overall; thymoma in 50% with Morvan syndrome	CSF
mGluR5	Ophelia syndrome, encephalitis	Confusion, psychiatric symptoms	29 years (6–75); 1.5:1	Normal findings (40) or nonspecific changes	60% Hodgkin's lymphoma	CSF
IgLON5	Anti-IgLON5 disease[b]	NREM and REM parasomnia with sleep apnea, brainstem dysfunction, movement disorders, cognitive impairment	62 42–91); 1:1	Normal findings or nonspecific changes (90)	No cancer association	CSF; present only in serum in a few patients
DPPX	Encephalitis with CNS hyperexcitability and gastrointestinal symptoms	Confusion, diarrhea, weight loss, myoclonus, tremors, hyperekplexia	52 years (13–76); 2.3:1	Normal findings or nonspecific changes (100)	<10% B-cell neoplasms	CSF
GlyR	PERM, stiff-person syndrome, hyperekplexia	Muscle rigidity, painful spasms, myoclonus	50 years (1–75); 1:1	Normal findings or nonspecific changes	20% thymoma, B-cell lymphoma, breast cancer	CSF

ADEM acute disseminated encephalomyelitis, *AMPAR* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, *CASPR2* contactin-associated protein-like 2, *CSF* cerebrospinal fluid, *CNS* central nervous system, *DPPX* dipeptidyl-peptidase-like protein 6, *FBDS* faciobrachial dystonic seizures, *GABA* γ-aminobutyric acid, *GABA$_A$R* GABA type A receptor, *GABA$_B$R* GABA type B receptor, *GlyR* glycine receptor, *IgLON5* Ig-like domain-containing protein 5, *LGI1* leucine-rich, glioma-inactivated 1, *mGluR5* metabotropic glutamate receptor 5, *MOG* myelin oligodendrocyte glycoprotein, *MRI* magnetic resonance imaging, *NMDAR* N-methyl-D-aspartate receptor, *NREM* non-rapid-eye-movement sleep, *PERM* progressive encephalomyelitis with rigidity and myoclonus, *REM* rapid-eye-movement sleep, *SCLC* small-cell lung cancer

[a] Data on brain abnormalities are based on T2-weighted MRI of the head with fluid-attenuated inversion recovery (FLAIR) sequences

[b] 75% of patients have a chronic course, but the remaining cases have a subacute evolution compatible with AE

Table 87.3 Minimal clinical requirements to suspect AE and mandates the determination of neural antibodies to confirm the diagnosis [11]

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits (or short-term memory loss), altered mental status[a], or psychiatric symptoms	
2. At least one of the additional criteria:	
(a)	New focal CNS findings
(b)	Seizures not explained by a previously known seizure disorder
(c)	CSF pleocytosis (>5 WBC/mm^3)
(d)	MRI features suggestive of encephalitis[b]
3. Reasonable exclusion of alternative causes	

[a] Altered mental status defined as decreased or altered level of consciousness, lethargy, or confusion

[b] Brain MRI hyperintense signal on T2/FLAIR sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter, or both compatible with demyelination or inflammation

common type of antibody-mediated AE [9]. Anti-NMDAR encephalitis mainly affects children and young adults (median age, 21 years), with a predominance of females (4:1) that becomes less evident before the age of 10 years and after the age of 45. About 40% of affected young women have an ovarian teratoma; in men and children, the association with tumors is less frequent. It can also develop in about 25% of patients with herpes simplex encephalitis several weeks after the viral infection is resolved; in these cases, there is compelling evidence that the viral infection triggers the AE (AE post-HSE) [5].

A definite diagnosis of anti-NMDAR encephalitis can be established in patients who develop any symptom of this disease along with the detection of antibodies against the GluN1 subunit of the NMDAR in CSF [11]. If CSF is not available, antibodies in the serum must be demonstrated with two different techniques (since serum testing is less reliable and associates with false positive or negative results in up to 20% of cases). Because antibody results are often delayed, a set of criteria for probable anti-NMDAR encephalitis have been developed in order to initiate immunotherapy before the antibody results are available. According to these criteria, patients must fulfill at least four of six core symptoms (psychiatric symptoms or cognitive dysfunction, speech disorder, seizures, abnormal movements, decreased level of consciousness, autonomic dysfunction) along with CSF pleocytosis or abnormal EEG. These criteria have good sensitivity (80% in adults and 90% in children) and specificity (96% in children), and the median time taken to fulfill them is approximately 2 weeks from symptom onset. The initial symptoms may differ in children and adults (adults have more psychiatric presentation, children have more seizures or abnormal movements), but 1 month after disease onset, regardless of the initial symptom presentation, most children and adults have a syndrome that combines several of the abovementioned symptoms [12]. Only in approximately 5% of patients, the disease may remain monosymptomatic (e.g., psychiatric symptoms). Additionally, about 85–90% of patients with anti-NMDAR encephalitis harbor mild to moderate CSF pleocytosis and/or elevated protein concentration; thus, although the CSF always contains NMDAR antibodies, and about 60% of patients have CSF-specific oligoclonal bands (OCB), the routine CSF analysis (cell count, glucose, and protein concentrations) can be otherwise completely normal. In 70% of cases, the brain MRI is normal or shows nonspecific, mild, or transient increased T2/FLAIR signal involving cortical, subcortical, or cerebellar regions, without or with mild contrast enhancement. More than 90% of patients have abnormal EEG studies that include focal or generalized slow activity and epileptic activity. A highly characteristic EEG pattern named extreme delta brush occurs in less than one-third of the patients.

Limbic Encephalitis

Limbic encephalitis (LE) can result from immune responses against several different neuronal antigens, both cell-surface and intracellular. Antibodies targeting leucine-rich, glioma-inactivated 1 (LGI1) account for the majority of cases of LE, followed by γ-aminobutyric acid (GABA) type B receptor (GABA_BR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR). [1] Patients are usually older than 45 years, while in very rare instances can affect children, and sex distribution varies with the type of antibody. The clinical picture of LE is characterized by rapid development (<3 months) of confusion, memory and cognitive deficits, psychiatric symptoms, and often seizures. The subacute development of inability to form new memories with relative preservation of the old ones (often called short-term memory loss) is considered the hallmark of the disorder. The brain MRI typically shows an increased T2/FLAIR signal in the medial aspect of the temporal lobes [11]. In some patients, the MRI is normal or shows unilateral changes; in these cases, the differential diagnosis includes edema from ongoing seizures, gliomas, and herpes simplex virus encephalitis. CSF analysis shows mild to moderate lymphocytic pleocytosis (usually <100 WBC/mm^3) in 60–80% of patients and elevated IgG index or OCB in approximately 50%. Antibody status is not needed for the definite diagnosis of LE if all criteria are fulfilled [11]. However, if the MRI does not demonstrate the indicated bilateral temporal involvement, specific antibody testing is mandatory in order to establish a definite diagnosis. The likelihood and type of underlying tumor and the response to treatment also differ according to the type of LE (see the chapter on paraneoplastic neurological disorders).

A subtype of LE, and probably the second most prevalent AE in adults, is the mentioned anti-LGI1 encephalitis. It preferentially affects older patients (median age, 60 years), with a slight male predominance, and may be preceded or initially accompanied by episodes of faciobrachial or crural seizures (described as faciobrachial dystonic seizures) in addition to hyponatremia in about 40% and 60% of patients, respectively. Main clinical features comprise memory and cognitive deficits, mood changes, focal seizures, and prominent sleep alterations, sometimes accompanied by features of peripheral nerve hyperexcitability [13]. Most anti-LGI1 patients do not have cancer and show substantial neurological improvement after immunotherapy [14].

Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is a monophasic, inflammatory disease of the CNS that mainly occurs in children and less frequently in adults younger than 40 years. It is likely the most frequent cause of AE in children and may be preceded by an acute systemic infection or vaccination. ADEM is characterized by encephalopathy (a mandatory diagnostic criterion) and other neurological signs, such as optic neuritis, myelopathy, and brainstem-cerebellar symptoms. MRI studies show multiple, large (>2 cm), and bilateral lesions involving both the white and gray matter on T2/FLAIR sequences, with or without contrast enhancement. Involvement of the thalamus, basal ganglia, or infratentorial lesions, including the spinal cord, occurs in at least 50% of cases. CSF analysis typically shows mild pleocytosis (<50 WBC/mm^3), but OCB are uncommon (less than 7% of all cases). Current diagnostic criteria of ADEM include the indicated set of clinical and MRI features and the exclusion of alternative disorders, especially multiple sclerosis [11].

MOG (myelin oligodendrocyte glycoprotein) antibodies are present in about 60% of children with ADEM, but they are not a requirement for the definitive diagnosis of ADEM [15]. Patients with ADEM and MOG antibodies are similar in age at presentation and type or severity of symptoms to patients without MOG antibodies. A small subset of patients with MOG-antibody-associated disorders (MOGAD) can present with predominant or isolated cortical FLAIR-hyperintense lesions with seizures [16]; these clinical-radiological features are not part of ADEM.

Antibody-Negative Autoimmune Encephalitis

Antibody-negative but probable AE (probable ANAE, also called probable "seronegative AE") defines a subgroup of patients with clinical features suggestive of AE (other than subsets of well-defined LE, ADEM that occur without antibodies) that after considering all diagnostic possibilities, focusing on the exclusion of alternative disorders and a well-substantiated absence of neural antibodies in CSF and serum, remain without a specific diagnosis. If these patients fulfill a set of criteria (including CSF, brain MRI, and brain biopsy; Table 87.4), they are categorized as probable ANAE [17].

Table 87.4 Criteria of autoantibody negative but probable AE (probable ANAE) [17]

Diagnosis can be made when all four of the following criteria have been met:
1. Rapid progression (<3 months) of working memory deficits (or short-term memory loss), altered mental status, or psychiatric symptoms
2. Exclusion of well-defined syndromes of AE (e.g., typical LE, ADEM, Bickerstaff brainstem encephalitis)
3. Absence of well-characterized autoantibodies in serum and CSF and at least two of the following:
(a) MRI abnormalities suggestive of AE[a]
(b) CSF pleocytosis and/or CSF-specific oligoclonal bands, elevated CSF IgG index, or both[a]
(c) Brain biopsy showing inflammatory infiltrates and excluding other disorders (e.g., tumor)
4. Reasonable exclusion of alternative causes

[a] Some inherited mitochondrial and metabolic disorders can present with symmetric or asymmetric MRI abnormalities and CSF inflammatory changes resembling an acquired autoimmune disorder

Neural Antibodies

In patients with suspected AE, the detection of specific neural (neuronal or glial) autoantibodies is important because it establishes a definitive diagnosis of AE, identifies immunological subtypes of LE, assists in the differential diagnosis of atypical clinical syndromes, directs the search for potentially involved comorbidities (e.g., systemic tumor), and contributes to formulate the treatment approach and prognosis. However, a current problem in the approach of AE is the high dependency on antibody testing, which leads to diagnostic delays and errors derived from false positive and false negative results. These pitfalls are in part associated with widespread screening using commercial kits and misinterpretation of the findings. Furthermore, the absence of antibodies does not exclude the immune-mediated cause. These limitations can be minimized following some recommendations: (1) Request the testing guided by the clinical features of suspected AE and carefully consider if the antibody results are the ones expected for the clinical syndrome, as not all neural antibodies have the same diagnostic value. Moreover, some antibodies are not routinely included in antibody panels. (2) Test always serum and CSF samples (CSF is more sensitive for most neural surface antibodies, see Table 87.2). (3) Be concerned for false results if neural surface antibodies are only detected in serum (except MOG or aquaporin 4 [AQP4] antibodies). (4) Disregard IgM or IgA class antibodies as diagnostic biomarkers, since only IgG neural antibodies have diagnostic significance. And (5) make sure that positive results are confirmed by two techniques, particularly if only serum is tested, the antibody titer is low, or the result is discordant with the clinical diagnosis. Concerning thyroid antibodies (i.e., thyroid peroxidase (TPO) antibodies), previously considered the hallmark of Hashimoto encephalopathy, their frequency in patients with AE and other autoimmune CNS disorders are not different from that observed in patients with alternative diagnoses or healthy persons. Hence, detection of TPO antibodies does not support the autoimmune etiology of a neurologic disorder and should not be used to implement or escalate immunotherapy [17].

Finally, the clinical suspicion should prevail, and CSF and serum of patients with syndromes highly suggestive of AE but initially negative for neural antibodies should be reexamined to ensure the appropriate repertoire of antibodies being tested (consider sending them to research laboratories).

Diagnostic Approach to AE

AE is considered in the differential diagnosis of any rapidly progressive encephalopathy of unclear etiology. The diagnostic workup should start with the clinical assessment. This includes the interval time of symptom progression, type of symptoms, patients' age and sex, and history of recent tumors or infections. In addition to the clinical assessment, brain MRI, EEG, and CSF studies play important roles in the diagnosis of AE. The MRI may show hyperintense lesions in T2/FLAIR suggesting an immune-mediated process, although in most AE it is normal or shows nonspecific inflammatory changes. Two exceptions are LE and ADEM in which the MRI, along with the indicated clinical features, has a major role in establishing the diagnosis of definitive LE and ADEM independently of the presence or absence of antibodies [11]. Cerebral FDG-PET might exhibit greater sensitivity than MRI, yet it lacks validation as a biomarker. EEG studies help to demonstrate focal or multifocal involvement in the absence of abnormalities in neuroimaging, encompassing focal or generalized slowing, seizures, or nonconvulsive status epilepticus. CSF analysis usually shows mild to moderate lymphocytic pleocytosis (<100 WBC/mm3) in 60–80% of cases and, in some instances, elevated IgG index with intrathecally restricted OCB; the protein concentration can be moderately increased or normal; however, the absence of inflammatory sings does not rule out AE (Table 87.3).

Current diagnostic guidelines for AE in both adults [11] and children [18] aim at facilitating the clinical recognition of AE based on indicated conventional clinical, radiological, and CSF studies to support initiation of immunotherapy without awaiting antibody results. Three features considered minimal requirements to suspect AE include the following: (1) subacute onset (≤3 months) of memory deficits, altered mental status, or psychiatric symptoms; (2) one or more among new focal CNS deficits, unexplained seizures, CSF pleocytosis, or MRI findings suggestive of encephalitis; and (3) reasonable exclusion of alternative disorders (Table 87.3). Fulfillment of these three requirements indicates that patients should be assessed for distinct types of AE and warrants the detection of neural antibodies that will confirm the diagnosis. A definitive diagnosis of AE can be given in the absence of neural antibodies in patients who meet the criteria of LE or ADEM. In the remaining cases, if the neural antibodies are negative, a diagnosis of probable ANAE can be done when the criteria described in Table 87.4 are rigorously fulfilled [17].

Management and Prognosis

AE are severe diseases that require intensive care support in about 50–70% of patients, sometimes for weeks or even months with life-threatening complications, but are potentially curable. In antibody-mediated AE, patients have predominant pathogenic mechanisms related to B cells, accompanied by mild to moderate brain T cell infiltrates. Therefore, the neurologic alterations are potentially reversible by eliminating the antibodies or the cells that produce the antibodies (B cells, plasma cells) [19]. Treatment recommendations are based largely on retrospective series and expert opinion (evidence grade B-C), since few clinical trials have been conducted [20]. The first step is an early and reliable diagnosis of AE to facilitate prompt initiation of immunotherapy, which is a recognized predictor of favorable outcome for all types of AE [12]. In addition to immunotherapy, it is important to address the presence of any immunologic trigger, such as a tumor or immune checkpoint inhibitor, when applicable. In these cases, the tumor should be removed and the immune checkpoint inhibitor discontinued [6]. Early transitioning from first-line immunotherapies (steroids, intravenous immunoglobulins, plasma exchange) to second-line immunotherapies (rituximab, cyclophosphamide) or even upfront use of these second-line immunotherapies is known to improve the outcome of patients who do not respond to first-line treatments and decrease the occurrence of relapses [12]. In ANAE patients, the use of immunotherapy should be carefully reassessed (e.g., not be escalated or not prolonged beyond 3–4 months) if the initial treatment approach is not effective [17].

The speed of recovery, degree of residual deficits, and frequency of relapses vary according to the type of AE. Nowadays, immunotherapy, symptomatic and supportive care, and removal of the immunological trigger (if identified) result in substantial improvement in about 80% of patients any time during the first 24 months of follow-up. The general outcome in children appears to be the same as in adults, although in some studies younger children tend to show a slower clinical recovery.

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Dr. Dalmau holds patents for the use of Ma2, NMDAR, GABAbR, GABAaR, DPPX, and IgLON5 as autoantibody tests.

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Autoimmune Dysautonomia

88

Judith Navarro-Otano

Abstract

Autoimmune dysautonomia can develop as a primary disorder or in the context of another systemic autoimmune disease. Autoimmune autonomic ganglionopathy causing pan-dysautonomia via antibodies against ganglionic nicotinic acetylcholine-receptor is the best-known example of these primary disorders. Although symptoms can seem unspecific, several clinical clues and objective autonomic reflex tests can help in the diagnosis and treatment.

Keywords

Autoimmune autonomic ganglionopathy · Nicotinic acetylcholine-receptor antibodies · Autonomic testing · Autoimmunity · Autonomic neuropathy

Introduction

The autonomic nervous system (ANS) plays a principal role in homeostasis maintenance and adaptation to the environment. ANS includes the sympathetic nervous system (SNS), parasympathetic nervous system (PNS), and enteric nervous systems (ENS). The preganglionic neurotransmitter for both SNS and PNS is acetylcholine, whereas the postganglionic one is noradrenaline for SNS and acetylcholine for PNS and SNS innervation to sweat glands. A complex central autonomic network and spinal cord descending pathways and ascending autonomic inputs are also recognized.

Autonomic disorders can manifest with both autonomic failure or hyperactivity involving cardiovascular (orthostatic intolerance, palpitations...), gastrointestinal (constipation, diarrhea, early satiety), secretomotor (anhidrosis, hyperhidrosis), pupillomotor (blurred vision, light intolerance), and genitourinary (erectile dysfunction, urinary retention, incontinence...) symptoms. Although some of these symptoms are quite unspecific, nowadays several tests have been described aimed at objective and quantifying the extent of autonomic neuropathy [1].

Over the past years, knowledge has been increasing regarding the interaction between the nervous and immune systems. SNS fibers have been detected in immunological organs, such as the thymus, spleen, and lymph nodes, and also some immune cells present adrenergic receptors. Increased circulating adrenaline and noradrenaline have been shown to activate pro-inflammatory cytokines and produce reactive oxygen intermediates, whereas sympathetic spleen innervation is linked to the anti-inflammatory reflex. The vagal nerve, the principal player of the PNS, reduces inflammation through the activation of cholinergic receptors on splenic macrophages [2–4].

In many inflammatory diseases, dysautonomia manifests as an imbalance in activity/reactivity of the sympathetic and parasympathetic divisions of the ANS.

Autoimmune dysautonomia can occur as a primary disorder or in the context of a systemic autoimmune disorder. There are no established diagnostic criteria for autoimmune autonomic disorders. From a clinical point of view, these entities should be suspected of autonomic disorders of acute or subacute onset or preceded by immunologic stimulus. Also, in a patient with known autoimmune diseases such as Sjögren syndrome or systemic lupus erythematosus, symptoms of autonomic dysfunction should be investigated.

Autoimmune Autonomic Ganglionopathy

Autoimmune autonomic ganglionopathy (AAG) is a rare disease of unknown prevalence. Patients are typically middle-aged females with an acute or subacute onset (mean age 45–61, female–male 2:1) [5]. There is a slowly progressive variant of AAG which can be very similar to other causes of

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Table 88.1 Most common symptoms in seropositive AAG based on published series [6–8]

Cardiovascular	Orthostatic hypotension	83–100%
Gastrointestinal	Early satiety-gastroparesis	23–50%
	Constipation	67–77%
	Diarrhea	16–31%
Genitourinary	Retention	50–77%
	Erectile dysfunction	64–100%
	Recurrent UTI	31%
Sudomotor	Anhidrosis	77%
Sicca syndrome	Dry mouth	66–100%
	Dry eyes	56–69%
Pupillomotor	Photophobia	46–69%

autonomic failure, mainly pure autonomic failure (neurodegenerative alpha-synucleinopathy).

Symptoms represent a widespread affectation of ANS including SNS, PNS and ENS dysfunction. Orthostatic intolerance including orthostatic hypotension is almost universally seen. Concomitant cholinergic dysfunction is prominent, including sicca syndrome, urinary retention, and blurred vision due to impaired pupil response [6–8]. See Table 88.1.

Formal autonomic testing should be performed to characterize the deficit and to establish the baseline prior to treatment. Testing includes heart rate response to deep breathing and the Valsalva maneuver (PNS), blood pressure response to Valsalva maneuver (SNS), and hemodynamic changes to passive head-up tilt. If available, sweating testing via thermoregulatory sweat test or quantitative sudomotor axon reflex test could provide valuable information.

Half of patients with AAG are found to have antibodies against the ganglionic α3 subunit—nicotinic acetylcholine receptor (gAChR) [9]. This receptor mediates transmission in all autonomic ganglia. There is a relationship between antibody levels and autonomic failure severity. Levels lower than 0.2 nmol/L are nonspecific and can be seen in healthy controls. Levels higher than 0.4 nmol/L are quite specific for AAG. Levels higher than 1 nmol/L are seen in severe cases [10, 11]. Laboratory studies in patients with suspected autoimmune dysautonomia should include the determination of antibodies against gAChR, anti-Hu, P/Q, and N-type voltage-gated calcium channel, voltage-gated potassium channel complex, and N-methyl-d-aspartate receptor.

In seropositive cases of AAG both iv immunoglobulin and plasma exchange have shown benefit as first-line therapy. Rituximab or mycophenolate mofetil could be administered as a second line. Mycophenolate mofetil, corticosteroids, and azathioprine could also be added if needed in combination with first-line therapy [5, 12]. Seronegative cases of AAG can also improve with immunomodulatory treatment, although experience is limited to case reports [13].

Management of autonomic symptoms with pharmacological and non-pharmacological options must be provided for every patient.

Other Autoimmune Autonomic Neuropathies

Whereas AAG involves SNS, PNS, and ENS, restricted forms have also been described [5, 12]. Acute cholinergic neuropathy, for example, is characterized by prominent sicca syndrome with hypotonic bladder, erectile failure, gastrointestinal dysmotility, and mydriasis. The laboratory could find low levels of gAChR antibodies.

Immune-mediated autonomic and sensory neuropathy is a rare disorder, often seronegative to gAChR antibodies and also lacking prominent sicca syndrome, genitourinary involvement, or pupilar abnormalities. Acute development of orthostatic hypotension, gastrointestinal dysmotility and sensory symptoms, and signs of large or small fiber neuropathy are described instead. These patients could respond to high dose iv steroids [14, 15].

Paraneoplastic autonomic syndromes have been described as associated with anti-Hu (mainly enteric neuropathy but also AAG phenotype or sensory and autonomic neuropathy), CRMP-5 (collapsing response mediator protein-5, AAG phenotype or enteric), and other paraneoplastic antibodies [11].

Autoimmune encephalitis can also present with autonomic features, such as episodic hyperactivity in encephalitis related to anti-contactin-associated protein-like 2 CASPR-2 antibodies. Morvan syndrome, a rare encephalopathy linked to antibodies to voltage-gated potassium channel complexes, is characterized by autonomic instability, including profuse sweating, hypertension, and cardiac arrhythmias.

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Cerebellar Autoimmune Diseases

89

Maria Sepúlveda and Francesc Graus

Abstract

Autoimmune cerebellar ataxias (ACA) encompass a heterogeneous group of disorders characterized by isolated or predominant cerebellar dysfunction caused by immune-mediated mechanisms. ACA include well-characterized entities with a clear trigger and/or association with specific neuronal antibodies, such as paraneoplastic cerebellar degeneration (PCD), cerebellar ataxia associated with glutamic acid decarboxylase antibodies (GAD), gluten ataxia (GA), or postinfectious cerebellar ataxia, as well as patients with suspected immune-mediated cerebellar ataxia but in the absence of malignancy and/or without known pathogenic antibodies. The best characterized autoimmune ataxia is PCD that, depending on the type of cancer, associates with different onconeural antibodies. Non-paraneoplastic ACA usually associate with GAD antibodies. GA is probably overdiagnosed as gliadin antibodies are not specific for the disease. Patients with ACA respond poorly to immunotherapy even when the associated antibodies are directed against neuronal surface antigens. However, a better prognosis is expected when immune-mediated therapeutic interventions are delivered during early stages when the cerebellar reserve still is preserved.

Keywords

Cerebellar ataxia · Autoimmune · Paraneoplastic cerebellar degeneration · Glutamic acid decarboxylase antibodies · Gluten ataxia

Introduction

Cerebellar ataxia is a common manifestation, and sometimes the most prominent, of many neurological diseases of different etiology, including genetic and acquired causes. The term autoimmune cerebellar ataxias (ACA) refers to a heterogeneous group of disorders in which the cerebellar ataxia is the only or the predominant symptom, and it is caused by immune-mediated mechanisms [1]. ACA include disorders with a clear trigger and/or association with well-characterized neuronal antibodies: paraneoplastic cerebellar degeneration (PCD), cerebellar ataxia associated with glutamic acid decarboxylase (GAD antibodies), gluten ataxia (GA), and postinfectious cerebellar ataxia. Unlike autoimmune encephalitis, most antibodies identified in ACA are directed against intracellular rather than neuronal surface antigens. There are no comprehensive prospective studies to show the prevalence of autoimmune cerebellar ataxias, but their frequency is probably low, and even for some entities, only a few patients have been published. In one study of 1500 patients with progressive ataxia, 25% had immune-mediated ataxia: 3% were paraneoplastic, 2% were associated with anti-GAD antibodies, and 20% were diagnosed as GA with gliadin antibodies [2]. This study has been criticized because, as commented below, the simple presence of gliadin antibodies cannot be used to make the diagnosis of gluten ataxia. Neuropathological studies indicate the Purkinje cell as the main target of the inflammation in ACA, with relative preservation of other neuronal cell types. Early diagnosis of ACA is important because the prompt introduction of immunotherapy, when cerebellar ataxia and/or cerebellar atrophy is mild, seems to be associated with a better prognosis [3].

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Clinical Features of Autoimmune Cerebellar Ataxias

Patients with ACA exhibit common clinical manifestations despite different etiologies. The onset of the ataxia is usually subacute (weeks) or acute (days) and less frequently chronic. The main clinical feature is gait ataxia, which influences standing and steady walking and is associated with mild limb incoordination and dysmetria, oculomotor ataxia, and scanning speech. Patients with non-paraneoplastic ACA sometimes show a personal or familial history of other autoimmune diseases, including Sjogren syndrome, pernicious anemia, type 1 diabetes mellitus (DM1), and vitiligo [4]. Brain MRI in ACA is frequently normal or shows mild vermian atrophy at diagnosis, which can be a clue for the differential diagnosis from degenerative or genetic cerebellar ataxias. Postinfectious cerebellar ataxia and ACA associated with particular antibodies (e.g., anti-Gluk2) usually show hyperintense T2 lesions in the cerebellum. As the disease progresses, cerebellar atrophy becomes more evident. CSF studies sometimes show inflammatory features with the presence of pleocytosis or oligoclonal bands. Finally, in most of the cases of ACA, the autoimmune etiology will be based on the detection of CSF and serum neuronal antibodies, although these antibodies may not always be pathogenic, and a reasonable exclusion of alternative causes [5].

Diagnostic Criteria

According to a task force comprising clinicians with an interest and extensive clinical experience in the management of ACA, the definitive diagnosis of ACA can be made when as follows: (1) the ataxia that fulfills criteria of PCD (see chapter on paraneoplastic neurological syndromes), (2) harbor antibodies which have been convincingly associated with ACA (mainly GAD), (3) history of a well-defined trigger (celiac disease, not just gliadin antibodies, or infection), and (4) cases not included above but who fulfilled the criteria proposed to define the ataxia as primary autoimmune cerebellar ataxia (PACA) (Table 89.1) [6]. More recently, another set of criteria has been proposed to circumvent the use of a new term—PACA—that probably it does not add clinical value (Table 89.2) [7].

Table 89.1 Primary autoimmune cerebellar ataxia (PACA) proposed criteria[a]

1. Predominantly subacute or acute pure cerebellar syndrome (gait ataxia that may be associated with variable degrees of limb incoordination, dysarthria, nystagmus, diplopia)
2. MRI at presentation normal or with primarily cerebellar vermian atrophy with (if available) reduced MR spectroscopy (NAA/Cr ratio) of the vermis
3. At least 2 of the following:
   (a) CSF pleocytosis and/or positive CSF-restricted IgG oligoclonal bands
   (b) History of other autoimmune disorders or family history of autoimmune disorders in first-degree relatives
   (c) Presence of antibodies that support autoimmunity but not yet shown to be either directly involved in ataxia pathogenesis or to be markers of ataxia with a known trigger
4. Exclusion of alternative causes made by an experienced neurologist or ataxia specialist (including other causes of immune ataxia, such as PCD, and those associated with well-characterized pathogenic antibodies)

[a] Patients must fulfil all four criteria

Table 89.2 Proposed diagnostic criteria for autoimmune cerebellar ataxias[a]

1. Presence of pure or predominant cerebellar syndrome (gait ataxia associated with variable degrees of limb incoordination, dysarthria, nystagmus, or diplopia), accompanied by normal brain MRI, or with minimal atrophy, at symptom presentation

AND

2. Presence of onconeural, GAD[b], septin 5 or mGluR1 antibodies[c]

OR

3. At least two of the additional criteria:
   (a) Subacute onset (rapid progression ≤3 months) of symptoms
   (b) History of other autoimmune disorders
   (c) CSF pleocytosis (WBC > $5/\text{mm}^3$) or positive IgG oligoclonal bands
   (d) MRI features suggestive of inflammation highly restricted to cerebellum
   (e) Presence of gliadin antibodies or autoantibodies against neuronal antigens with limited/preliminary information
   (f) Infectious episode in the previous three weeks or recent cancer diagnosis (<2 years)

AND

4. Exclusion of other causes of cerebellar ataxia

[a] Definite ACA: patients fulfill criteria 1, 2, and 4; Probable ACA: patients fulfill criteria 1, 3, and 4

[b] Serum GAD antibodies must have high titers and CSF intrathecal synthesis of anti-GAD should be confirmed

[c] For patients with pure or predominant ataxia and GAD, mGluR1, septin5 or onconeural antibodies, the number of reported cases or evidence for pathogenicity allow classifying the disorder as definite ACA

Paraneoplastic Cerebellar Degeneration

Paraneoplastic cerebellar degeneration (PCD) represents a well-characterized group of cerebellar ataxias associated with cancer. In PCD cases, the autoimmune response would be triggered by the tumor. The presence of characteristic onconeural autoantibodies is not only diagnostic for PCD but also provides a clue to the specific type of the underlying tumor. Patients develop acute/subacute unsteady gait that may be preceded by prodromal clinical symptoms such as dizziness, nausea, and vomiting. Subsequently, the gait ataxia is followed by a rapid development of pancerebellar symptoms that in a few weeks leaves patients severely disabled, unable to perform the normal activities of daily living. Dysphagia can be severe and require feeding via nasogastric tube or percutaneous endoscopic gastrostomy. Oscillopsia can also be very disabling and prevents the patient from reading or watching television due to the presence of nystagmus, usually downbeating, or saccadic incoordination. Brain MRI at onset is usually normal and, over the ensuing months, shows a variable degree of cerebellar atrophy. In a few patients, MRI at onset shows generalized swelling of the cerebellum or gadolinium enhancement of the cerebellar folia or meninges. 18-Fluorodeoxyglucose positron emission tomography (FDG-PET) scanning reveals intense hypermetabolism in the cerebellum and diffuse hypometabolism in the rest of the brain at the initial stages of PCD, even when the brain MRI is normal. However, the evidence reported is limited, and more studies are needed to confirm the potential value of FDG-PET in the diagnosis of ACA. CSF examination may show mild pleocytosis (<50 lymphocytes/μL), IgG oligoclonal bands, and elevated 14-3-3 protein levels, which may lead to a false diagnosis of Creutzfeldt–Jakob disease.

The most valuable test to confirm PCD is the determination of onconeural antibodies, which are also useful in guiding the search for the tumor. In Table 89.3 are listed the main onconeuronal antibodies associated with PCD as well as less common antibodies, which have been described in a few patients with PCD. Pathological investigations of patients, affected by PCD with independence of the associated antibody, have shown severe and extensive loss of Purkinje cells, with granular cells and neurons of the dentate nucleus relatively spared. The presence of inflammatory infiltrates is variable and probably depends on the patients' survival time (PCD patients with longer survival are less likely to have inflammatory infiltrates) [8].

Table 89.3 Neural antibodies in paraneoplastic cerebellar degeneration

Antibody	Tumor	Clinical features
Yo (PCA1)	Ovary, breast	Isolated cerebellar syndrome
Hu (ANNA1)	SCLC Less common: NSCLC, neuroendocrine tumors	Frequent involvement of other CNS areas(encephalomyelitis)
CV2 (CRMP5)	SCLC Less common: Thymoma	Frequent association with neuropathies and involvement of other CNS areas (encephalomyelitis)
SOX1	SCLC	May associate LEMS
VGCC	SCLC	May associate LEMS
Tr (DNER)	Hodgkin lymphoma	Isolated cerebellar syndrome
Ri (ANNA2)	Breast Less common: SCLC, NSCLC, ovary, bladder	Brainstem involvement with opsoclonus, jaw dystonia, and laryngospasm
Ma2/ma	Testicular germ-cell Less common: NSCLC, lymphoma	Frequent association with limbic and diencephalic encephalitis
PCA2	SCLC Less common: NSCLC, breast	Frequent association with neuropathies and involvement of other CNS areas(encephalomyelitis)
KLHL11	Testicular germinoma	Brainstem encephalitis frequently associated sensorineural hearing loss
Amphiphysin	SCLC	Association with extra cerebellar symptoms (encephalomyelitis)
Antibodies with limited information		
TRIM 46, 9, and 67	NSCLC, SCLC, melanoma	46—Cerebellar ataxia 9, 67—Cerebellar ataxia, encephalomyelitis
mGluR2	Small-cell tumor, sarcoma	Isolated cerebellar syndrome
PKC gamma	NSCLC, tonsil, GI tumor	Isolated cerebellar syndrome
PRG5	NSCLC	Isolated cerebellar syndrome
CARP VIII	Melanoma, ovary, breast	Isolated cerebellar syndrome
RSG8	Lymphoma	Isolated cerebellar syndrome

ANNA anti-nuclear neuronal antibody, *CARP* carbonic anhydrase-related protein, *CRMP5* collapsing response mediator protein 5, *DNER* delta/notch-like epidermal growth factor-related receptor, *GI* gastrointestinal, *KLHL11* Kelch-like protein 11, *LEMS* Lambert–Eaton myasthenic syndrome, *mGluR2* metabotropic glutamate receptor 2, *NSCLC* non-small-cell lung cancer, *PCA* Purkinje cell antibody, *PKC* protein kinase C, *PRG5* plasticity-related gene 5, *RSG8* regulator of G-protein signaling 8, *SCLC* small-cell lung cancer, *TRIM* tripartite motif-containing protein, *VGCC* voltage-gated calcium channel

Non-Paraneoplastic ACA Associated with Neuronal Antibodies

Cerebellar Ataxia and GAD Antibodies

GAD is an enzyme that catalyzes the conversion of glutamic acid to gamma-aminobutyric acid (GABA), the most important central nervous system (CNS) inhibitory neurotransmitter. In the brain GAD has two isoforms: GAD65 and GAD67. GAD antibodies were initially identified in patients with DM1 and in patients with stiff-person syndrome, a disorder of the CNS characterized by progressive muscle rigidity with superimposed painful spasms [9]. Later, high levels of GAD antibodies were also identified in a subset of patients with cerebellar ataxia, supporting an autoimmune pathogenesis of the cerebellar syndrome [10]. It is important to notice that serum and CSF titers of GAD antibodies are more than 100-fold higher in anti-GAD ataxia, compared to those of patients with DM1. Anti-GAD ataxia mostly affects women in their 60 s, with subacute onset of symptoms, although in about 60% of patients, the clinical course is chronic and progresses over several years. Isolated gait ataxia is the most common presenting symptom, which is later accompanied by limb ataxia, dysarthria, and nystagmus. Cerebellar symptoms may be preceded by short periods of dizziness or self-limited episodes of diplopia, dysarthria, or gait ataxia. Anti-GAD ataxia is sometimes associated with extracerebellar symptoms, including epilepsy and stiff-person syndrome. DM1, particularly late-onset DM1, is frequently observed along with other autoimmune conditions, such as autoimmune thyroid diseases and pernicious anemia. Most patients do not have cancer, although a cancer association has been reported in a few cases [11]. The CSF shows oligoclonal bands in 70% of the patients, with normal protein concentration, and > 70% have intrathecal synthesis of GAD antibodies. Brain MRI shows normal or atrophic changes depending on the duration of illness. Antibodies against GAD65 are invariably present in serum and CSF, whereas antibodies against GAD67 are found in 80% of sera and 100% of CSF. The diagnosis of anti-GAD ataxia requires the identification of GAD antibodies in CSF and, ideally, the detection of intrathecal synthesis of GAD antibodies. In those cases, with positive GAD antibodies only in serum, even at high levels, diagnosis of anti-GAD ataxia should be taken with caution because high titers of GAD antibodies have been described in a few patients with isolated DM1, and low titers are found in 1–8% of normal subjects [9].

Non-Paraneoplastic ACA and Infrequent Neuronal Antibodies

Different antibodies have been described in patients with cerebellar ataxia in the absence of cancer, suggesting an autoimmune pathogenesis, although a direct pathogenic effect has not been established. Most of these antibodies have been found in a few patients or the clinical spectrum is sometimes not restricted to cerebellar ataxia (Table 89.4). We briefly comment here the two antibodies which in our opinion should be considered as relevant as GAD or onconeural antibodies for the diagnosis of ACA because they could be pathogenic. Metabotropic glutamate receptors (mGluR) are a family of cell surface G-protein-coupled receptors that bind glutamate and play a significant role in synaptic transmission and neuronal excitability. Metabotropic glutamate receptor 1 (mGluR1) antibodies were the first to be identified in patients with cerebellar ataxia in the early 2000s. In a literature review of 30 patients with mGluR1 antibodies, the median age was 55 years (range: 6–81 years) and 43% were female. Three patients had a remote history of Hodgkin's disease or T-cell lymphoma. The brain MRI was normal or showed cerebellar atrophy, and CSF studies were usually normal. Clinical improvement was observed in 10 (40%) of patients after treatment with various types of immu-

Table 89.4 Infrequent antibodies against neuronal targets in non-paraneoplastic ACA

Antibody	Clinical features	Antigen location	Response to immunotherapy
ARHGAP26	May associate polyneuropathy	Intracellular	Poor
ITPR-1	Aprox. 40% present with cerebellar ataxia Peripheral neuropathy	Intracellular	Poor
Neurochondrin	Chronic cerebellar/brainstem syndrome	Intracellular	No improvement
CASPR2	Paroxysmal ataxic episodes lasting minutes to hours Episodes may antedate the onset of encephalitis	Extracellular	Improvement
Sez6l2	Subacute gait ataxia May associate parkinsonism	Extracellular	Poor
AP3B2	Progressive gait ataxia Peripheral neuropathy	Intracellular	Poor
Homer-3	Subacute cerebellar syndrome	Intracellular	No improvement
Gluk2	Acute cerebellitis (2 patients had obstructive hydrocephalus)	Extracellular	Improvement

ARHGAP26 rho GTPase-activating protein 26, *ITPR1* inositol 1,4,5-trisphosphate receptor type 1, *Caspr2* contactin-associate protein-2, *SEZ6L2* seizure-related 6 homolog like 2, *AP3B2* adaptor protein-3B2, *Gluk2* glutamate kainate receptor, *RCC* renal cell cancer, *SCLC* small cell lung cancer

notherapy [12]. Intrathecal injection of sera from patients with ataxia and mGluR1 antibodies to mice caused transient gait ataxia suggesting the antibodies could be pathogenic.

Antibodies against septin-5 have been identified in the serum and CSF of eight patients with a rapidly progressive cerebellar syndrome with prominent eye movement symptoms (oscillopsia or vertigo). Brain MRI, available in seven patients, was normal in 4, showed cerebellar atrophy in two, and cerebellar diffuse T2 hyperintensity in one. Improvement occurred in 5/6 patients (spontaneously in one), after immunotherapy. Septin-5 is a guanosine triphosphate (GTP)-binding protein expressed in presynaptic terminals. Like amphiphysin, septin-5 is exposed to the extracellular space during exocytosis and therefore has the potential to interact with the antibody [13].

Cerebellar Ataxias Not Associated with Neuronal Antibodies

Gluten Ataxia

Gluten ataxia (GA) was defined by the association of sporadic cerebellar ataxia with antigliadin antibodies, independently of the existence of a proven coeliac disease, after the exclusion of other causes of ataxia [14]. GA has been proposed as an immune-mediated disease, triggered by the ingestion of gluten in susceptible individuals. However, gliadin antibodies can also be detected in 5–12% of healthy individuals and up to 37% of patients with familial cerebellar ataxias, and there is no clear evidence that gliadin or other antibodies present in the serum of patients with cerebellar ataxia recognize neuronal surface antigens, so whether autoimmune mechanisms mediate the cerebellar ataxia in people with gluten sensitivity remains unclear.

GA has been reported as the most frequent cause of sporadic progressive cerebellar ataxia, with a frequency ranging from 11% to 41% in different series of patients with cerebellar ataxia [2]. However, this frequency is probably an overestimation as not all patients with only gliadin antibodies can be defined as GA. On the other hand, there are isolated cases of cerebellar ataxia with clinical symptoms of celiac disease in whom no other explanation of the cerebellar ataxia is found. These patients are in their 40–50 s, without sex preference. Clinical presentation is gait ataxia of chronic or insidious onset, followed by dysarthria and lower limb ataxia. Most patients experience prominent nystagmus. Other systemic autoimmune disorders, mainly hypothyroidism, DM1, and pernicious anemia, are commonly present. CSF analysis shows no inflammatory changes and brain MRI almost always shows cerebellar atrophy that in the inferior vermix and cerebellar hemispheres. Autopsy studies show severe loss of Purkinje cells, along with variable degrees of lymphocyte infiltrates, gliosis, and microglial activation [15]. If these patients have a cerebellar ataxia caused by mechanisms linked to the celiac disease or develop an associated ACA as an expression of the autoimmune disorder background (as they may have pernicious anemia or vitiligo) is presently unclear.

Postinfectious Cerebellar Ataxia

Postinfectious cerebellar ataxia is caused by inflammation induced by not well-known immune-mediated mechanisms triggered by the infection. This entity is the most frequent cause of cerebellar ataxia in children, but adults are rarely affected. Postinfectious cerebellar ataxia affects young children after an episode of infection, usually viral infection, most commonly varicella. Other viruses, such as Epstein-Barr virus, Coxsackie virus, influenza A and B virus, and parainfluenza virus, can be involved. The latency between infection and the onset of acute cerebellar ataxia usually is 1–2 weeks after a viral infection. The development of cerebellar ataxia after vaccination or bacterial infections is much less frequent. Brain MRI is normal, and patients experience a benign clinical course. There is no evidence that steroids or intravenous immunoglobulins shorten the recovery time [16].

The term “acute cerebellitis” is used when the patient develops a more severe, sometimes life-threatening disorder associated with cerebellar lesions in the MRI. Patients develop acute-onset afebrile gait ataxia, meningeal signs, high intracranial pressure with or without extracerebellar manifestations, such as temporary clouding of consciousness, seizures, altered mental status (e.g., extreme irritability), or extracerebellar focal signs. CSF examination shows moderate pleocytosis. Brain MRI shows hyperintense lesions in both cerebellar hemispheres on T2-weighted and fluid-attenuation inversion recovery (FLAIR) sequences [17]. Gadolinium enhancement of the cerebellar leptomeninges is also a common feature. In these patients, the long-term prognosis is less favorable, and almost half of them have residual neurological deficits. Steroids are routinely used in patients with acute cerebellitis, particularly if there are symptoms of intracranial hypertension. In almost 25% of patients, an external ventricular drainage or decompressive craniectomy is required to resolve the obstructive hydrocephalus and to prevent cerebellar herniation [18].

Treatment Considerations

There are no large-scale randomized studies comparing therapeutic strategies in ACA patients. In general, immunotherapy is recommended. Immunotherapies should be introduced in the early stages of the disease when the cerebellar reserve is still preserved [19]. However, the demonstration of neural antibodies does not necessarily imply a good response to immunotherapy.

In those cases where ACA is caused by a known trigger, priority should be given to the treatment of the underlying condition. Treatment of GA requires adherence to a strict gluten-free diet [20]. For those cases with PCD, immediate attention to the treatment of neoplasm should be the first therapeutic objective. In addition to surgical excision or chemotherapy and radiotherapy, various types of immunotherapies (corticosteroids, intravenous immunoglobins, plasmapheresis, immunosuppressants, and rituximab, alone or in combination) have been used, without significant differences in the response. The prognosis of PCD is generally poor, and the response to immunotherapy following removal of the neoplastic lesion is often disappointing. It is considered that fewer than 10% of patients with PCD are likely to respond to immunotherapy [1]. In patients with ataxia associated with GAD antibodies, response to immunotherapy is usually suboptimal. In a retrospective study of 25 patients with anti-GAD ataxia and a median follow-up of 5.4 years, only 11 (44%) patients had a modified Rankin score <3 at the last visit, indicating a restriction of lifestyle. In the same study, a sustained clinical improvement after immunotherapy was observed in 7/20 (35%) patients. Patients who had a subacute onset of cerebellar symptoms and early initiation of immunotherapy were more likely to respond to the treatment [10].

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90

Autoimmune Disturbances of Sleeping

Carles Gaig and Amaia Muñoz-Lopetegi

Abstract

Sleep disorders are common in some neurological autoimmune diseases like narcolepsy, neuromyelitis optica spectrum disorders, and several types of autoimmune encephalitis associated with antibodies against neuronal surfaces or intracellular proteins. Brain areas that generate and regulate the sleep-wake cycle are usually affected in these neurological diseases, leading to prominent and distinctive sleep disorders, including hypersomnolence, insomnia, parasomnias, and sleep breathing difficulties. A proper identification of these sleep disorders can be important to diagnose some of these neurological autoimmune diseases.

Keywords

Sleep disorders · Autoimmune encephalitis · Narcolepsy · Hypersomnolence · Parasomnia · REM sleep behavior disorder · Neuromyelitis optica spectrum disorders · Anti-NMDAR encephalitis · Anti-IgLON5 disease · Anti-Ma2 encephalitis

Introduction

Sleep disorders are common in some neurological autoimmune diseases as the underlying immunological process often affects brain areas that generate and regulate the sleep and wake cycle, such as the hypothalamus or certain brainstem nuclei. The four major types of sleep disorders (hypersomnolence, insomnia, parasomnia, and sleep-disordered breathing) can occur in these neurological autoimmune diseases, being usually prominent and severe. The sleep disorder can be the initial manifestation, which often persists beyond the acute phase, or it may be the main symptom or even a distinctive feature of the disease [1]. In some instances, however, the sleep problem can be overshadowed by other more disabling neurological symptoms, such as cognitive impairment, behavioral abnormalities, seizures, gait difficulties, or movement disorders. In this chapter, we will discuss the sleep disorders occurring in narcolepsy, neuromyelitis optica spectrum disorders (NMOSD) and several types of autoimmune encephalitis associated with antibodies against proteins of the neuronal surface (e.g., ion channels or receptors) or intracellular proteins [2, 3]. Special attention will be paid to the clinical evaluation and diagnosis of these sleep disorders as their prompt recognition can help diagnose the autoimmune disease (Table 90.1) [1].

Insomnia in these autoimmune neurological disorders (e.g., in anti-NMDAR or anti-Caspr2 encephalitis) is usually severe and often associated with loss of the circadian sleep-wake rhythm. Hypersomnolence can manifest as either excessive daytime sleepiness (EDS) or hypersomnia in narcolepsy, NMOSD, or anti-MA2 encephalitis [1, 3–6]. EDS is characterized by an inability to stay awake during the normal wake period of the day, with episodes of an irrepressible need to sleep or unintended lapses into sleep. In contrast, hypersomnia is defined by an excessive quantity of sleep (at least 10 h of sleep duration over 24 h of the day). Therefore, EDS and hypersomnia are two different problems that may coexist or not in the same patient (and hypersomnolence is the general term to encompass both symptoms). REM sleep behavior disorder (RBD) is a parasomnia clinically characterized by nightmares (e.g., being attacked or robbed) and violent behaviors in which the patients are enacting their dreams (e.g., punching, jumping out of bed, shouting). When recorded in video-polysomnography (VPSG), these behaviors occur during a REM sleep that has lost its physiologic atonia. RBD can occur in several neurological conditions such as Parkinson disease or brainstem lesions (e.g., infarctions), or be secondary to medications (mainly antidepressants). RBD can also occur in anti-LGI1 encephalitis,

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Table 90.1 Sleep disorders in autoimmune neurological disorders

	Age, gender and associated features	Main neurological symptoms	Sleep disturbances	Video-PSG and sleep studies
Narcolepsy	Children and young adults, similar gender distribution HLA DQB1*06:02 (>95%) Low CSF hypocretin-1 levels (≤110 pg/mL)	Chronic hypersomnolence associated with cataplexy	Intense excessive daytime sleepiness. Short refreshing naps Sleep paralysis and hallucinations Nocturnal sleep disturbed by frequent arousals (50%)	Normal NREM sleep RBD (25–30%) Increased risk of obstructive sleep apnea if overweight MSLT shows reduced sleep latency and ≥2 SOREMPs
Neuromyelitis optica spectrum disorders	Middle age, similar gender distribution Antibodies against aquaporin-4 (75–80)	Subacute visual loss and transverse myelitis with large segments of the spinal cord involved. Bouts of intractable vomiting and hiccoughs	Severe hypersomnia, with narcolepsy features (cataplexy, low CSF hypocretin-1 levels)	MSLT shows a reduced sleep latency and ≥2 SOREMPs
Anti-M2 encephalitis	Middle age, males > females (2:1), testicular germ-cell tumor, lung cancer (~100%) Antibodies against Ma2	Subacute memory loss, seizures, parkinsonism, gaze palsy, hypothalamic dysfunction (diabetes insipidus), hypersomnia	Severe hypersomnia, with narcolepsy features (cataplexy, low CSF hypocretin-1 levels)	Abnormal NREM sleep architecture in some patients, with absence of sleep spindles and K complexes RBD can be present MSLT shows a reduced sleep latency and ≥2 SOREMPs
Anti-NMDA receptor encephalitis	Children and young women Ovarian teratoma (~50%) Antibodies against NMDA receptor	Acute psychosis, amnesia, confusion, seizures, movement disorders, catatonia, autonomic instability, coma	Severe insomnia in the early phase Hypersomnia after recovery	Confusional arousals form NREM sleep in the recovery phase
LGI1 encephalitis	Elderly or middle age, males > females (2:1), thymoma, lung cancer (~10%) Antibodies against LGI1 HLA DRB1*07:01 and DQA1*02:01 (90–100%)	Subacute limbic encephalitis with memory loss and confusion, faciobrachial dystonic seizures, focal and secondary generalized epileptic seizures	Mild to severe insomnia Mild to moderate daytime sleepiness Hypersomnia (15%)	Low sleep efficiency, reduced/absent NREM N3 stage and REM sleep RBD (~50%) Nocturnal seizures
Caspr2 encephalitis	Older males, thymomas, small cell lung cancer (~5%) Antibodies against Caspr2 HLA DRB1*11:01 positive (50%)	Subacute sleep disorder with insomnia, dysautonomia and neuromyotonia (Morvan syndrome), cognitive impairment, seizures, cerebellar symptoms	Severe insomnia with loss of the circadian sleep-wake pattern with episodes of dream-enacting behaviors (*oneiric stupor*)	Theta activity with brief intrusions of REM sleep (stage N1-REM or subwakefulness) absence of K complexes, spindles, and slow wave activity (disappearance of stages N2 and N3) Short periods of REM sleep without atonia
Anti-IgLON5 disease	50–80 years Affects similarly both genders Antibodies against IgLON5 HLA DRB1*10:01 and DQB1*05:01 (60–70%)	Chronic sleep disorder with parasomnia and sleep breathing disorder associated with bulbar symptoms (dysarthria, dysphagia), gait instability, chorea, and cognitive impairment	Frequent vocalizations, movements, and behaviors during sleep. Complaints of non-restorative and poor-quality sleep witnessed sleep apneas with a loud respiratory noise. Mild to moderate daytime somnolence can occur	Abnormalities in NREM sleep initiation with undifferentiated NREM sleep and poorly structured N2 sleep with frequent vocalizations, movements, and complex behaviors. Periods of normal NREM sleep (stages N2 and N3) are present REM sleep without atonia with frequent limb and body jerks Stridor (due to vocal cord palsy) and frequent obstructive sleep apnea. Nocturnal hypoventilation can occur

CSF cerebrospinal fluid, *MSLT* multiple sleep latency test, *RBD* REM sleep behavior disorder, *SOREMPs* sleep onset REM periods anti-IgLON5 disease, and narcolepsy. The pathophysiology of RBD is related to a dysfunction of the lower brainstem nuclei that modulate REM sleep (i.e., subcoeruleus nucleus or magnocellularis nucleus). Other parasomnias seen in autoimmune neurological disorders (anti-Caspr2 encephalitis or anti-IgLON5 disease) are characterized by a severe abnormality in sleep architecture with associated motor activation and abnormal behaviors. Sleep breathing disorders can include hypoventilation, obstructive sleep apneas (OSA), and stridor during sleep (e.g., anti-IgLON5 disease). Stridor is a high-pitched respiratory sound produced by turbulent airflow through a narrow glottic space secondary to vocal cord palsy that increases or worsens during sleep [1].

The assessment of all these sleep problems requires a systematic sleep anamnesis that has to be obtained not only from patients but also from bedpartners, relatives, or caregivers, as patients may not be aware of some of their problems while asleep (e.g., abnormal sleep behaviors or sleep breathing difficulties). It is important to remind that when other neurological symptoms are more prominent and severe, patients and bedpartners may not spontaneously report sleep problems so that specifically asking about them is crucial. This sleep history, if necessary, has to be complemented with sleep studies, mainly a nocturnal VPSG [1].

Narcolepsy

Narcolepsy is a chronic neurological disorder characterized by EDS with symptoms of REM sleep dysregulation including cataplexy, sleep paralysis, sleep-related hallucinations, and disturbed nocturnal sleep [3]. The disease typically develops during childhood, adolescence, or early adulthood, with an overall estimated prevalence between 10 and 70 cases per 100,000 inhabitants. Cataplexy is a distinctive symptom of narcolepsy characterized by episodes of sudden loss of muscle tone lasting few seconds (rarely few minutes) typically triggered by emotions (e.g., laughter, satisfaction, or other positive emotions; negative emotions like anger and fear rarely trigger cataplexy). Loss of muscle tone can be mild and focal (e.g., loss of facial and neck tone with a drop of the head), or intense and generalized (e.g., causing to fall down). Cataplexy can be misdiagnosed as syncope or epileptic seizures, but consciousness is preserved during the episode. Asking for cataplexy and properly identifying it in a patient complaining of EDS is essential to suspect a narcolepsy [3].

Narcolepsy is caused by a selective loss of the hypocretin-producing neurons in the posterolateral hypothalamus, leading to a deficiency of this neurotransmitter with an important function to maintain wakefulness and suppress REM sleep. Because of a tight association with the HLA DQB1*0602 allele (present in more than 95% of patients), an immune mediated loss of these neurons is hypothesized [1]. Moreover, recently autoreactive CD4+ and CD8+ T cells that specifically target antigens expressed by hypocretin producing neurons have been identified in patients with narcolepsy [6].

The diagnosis of narcolepsy can be confirmed with a multiple sleep latency test (or MSLT, consisting of 20-min nap opportunities, 5 times across the day), showing a reduced mean sleep latency (< 8 min) and two or more sleep onset REM periods (SOREMPs). The gold standard for narcolepsy diagnosis, however, is a CSF analysis demonstrating undetectable or very low hypocretin-1 levels (≤110 pg/mL, normal values >200 pg/mL). Treatment of narcolepsy is symptomatic. Patients do not improve with immunotherapy, probably because the diagnosis of the disease is usually made several years (often up to 5–10 years or even more) after symptoms onset, when the neuronal loss is already established and the immunological attack is no longer active [3].

Neuromyelitis Optica Spectrum Disorders (NMOSD)

NMOSD comprehend a group of demyelinating central nervous system syndromes distinct from multiple sclerosis, characterized by optic neuritis and/or longitudinally extensive transverse myelitis [4, 5]. The autoimmune inflammatory attack to the optical nerve and spinal cord tends to be severe and recurrent, often with incomplete recovery and substantial morbidity and mortality if not diagnosed and treated early. Approximately 75% of the patients have antibodies against aquaporin-4, a water channel expressed on astrocytes. Bilateral hypothalamic demyelinating lesions can occur in some patients, as aquaporin-4 is highly expressed in this diencephalic brain area, causing acute-onset, prominent hypersomnia with features that are typical of narcolepsy, such as cataplexy, undetectable CSF hypocretin-1 levels, and multiple SOREMPs in MSLT. The hypothalamic demyelination as well as the hypocretin deficiency and hypersomnia are reversible in most cases with immunotherapy [4, 5, 7].

Anti-Ma2 and Paraneoplastic Encephalitis

This is a paraneoplastic encephalitis associated with testicular or lung carcinomas and Ma2 antibodies that are directed against intraneuronal proteins [8]. The inflammatory process affects limbic, diencephalic, and brainstem structures (hyperintensities on these brain areas are often seen in brain MRI), manifesting clinically as subacute memory loss, seizures, parkinsonism, gaze palsy, and symptoms of hypothalamic dysfunction (e.g., diabetes insipidus, hyperthermia). Up to one-third of the patients present sleep problems, mainly severe hypersomnia that associates features typical of narcolepsy like cataplexy, reduced hypocretin-1 levels in CSF, or multiple SOREMPs in the MSLT [8–10]. Postmortem examination in patients with anti-Ma2 encephalitis has shown inflammatory infiltrates with cytotoxic CD8+ T lymphocytes in the hypothalamus with loss of the hypocretin-producing neurons, which explains this secondary narcolepsy [11]. Additional sleep abnormalities occurring in this encephalitis related to the hypothalamic and brainstem inflammation are an altered sleep architecture with absence of sleep spindles in the VPSG or the development of RBD [9, 10]. The prognosis of this paraneoplastic encephalitis is usually poor and hypersomnia and other sleep disorders often do not improve with immunotherapy and treatment of the primary tumor, probably due to the irreversible neuronal loss.

Anti-NMDA Receptor Encephalitis

Anti-NMDA receptor encephalitis (NMDARe) is characterized by acute-onset, severe neurological and psychiatric symptoms that usually affect children and young adults, predominantly women, and may be associated with ovarian teratomas. Insomnia is present in up to 90% of the patients with NMDARe. It appears during the initial stages of the disease, sometimes preceding any other symptoms by days or even weeks, and progressively worsens in pace with other symptoms. At the peak of the disease, when the attention is coped by severe neuropsychiatric symptoms of disorganized behavior, psychosis, dyskinetic and choreiform movement disorders, or seizures, patients also suffer a severe reduction of sleep time throughout the 24-hour period [1, 2]. The whole picture is often misinterpreted as the debut of a primarily psychiatric disease (e.g., schizophrenia, bipolar disorder), in which insomnia is frequent as well [12]. However, atypical features like the acute onset and the progressive addition of severe psychiatric and neurologic symptoms, as well as unresponsiveness to neuroleptic and other drugs, should raise suspicion of NMDARe and prompt a CSF analysis to search for NMDAR antibodies and start immunotherapy at the quickest.

During recovery (after several weeks and even months of hospitalization), most patients transition into a period of hypersomnia, with increased 24-h sleep, without other features typical of narcolepsy. The hypersomnia is enclosed in the context of a global shift in the disease-related symptoms, from disorganized behaviors in the acute stage to predominantly apathetic and inhibited behaviors during recovery, sometimes with hyperphagia, hypersexuality, in addition to hypersomnia and cognitive symptoms, that last for months [12]. Sleep studies during the acute stage of the disease are difficult to conduct and interpret due to many factors such as artifacts derived from severe agitation and involuntary movements or interfering medications (including sedating drugs during ICU admissions). During the recovery stage, VPSG studies have shown normal sleep architecture with well-identifiable sleep stages. Some patients, without a previous history, develop NREM sleep arousal disorders or parasomnia that manifests as confusional arousals, most times mild, and constituting a finding of unknown clinical and pathophysiological significance [1, 12].

Anti-LGI1 Encephalitis

Anti-LGI1 encephalitis (LGI1e) usually presents as a limbic encephalitis, with acute or subacute cognitive impairment, behavioral and psychiatric symptoms, and epileptic seizures. Additional features that distinguish LGI1e from other limbic encephalitis are the faciobrachial dystonic seizures (FBDS; 30–50% of the patients) and hyponatremia [1, 2]. The most frequent sleep symptom is insomnia, reported by 45–65% of the patients. It may be severe, usually appears early in the disease course and is characterized by an inability to initiate or sustain sleep at night. It may be accompanied by secondary EDS. Instead, about 15% of the patients may develop hypersomnia. A systematic sleep anamnesis reveals dream-enacting behaviors typical of RBD in 50% of the patients (Fig. 90.1). Series or case reports with VPSG recordings show distorted sleep architecture with low sleep efficiency and reduced or absent NREM N3 and REM sleep. Half of the patients have RBD confirmed by lack of normal muscle atonia associated with typical behaviors. Focal epileptic seizures and FBDS can occur during sleep as well and contribute to sleep fragmentation [1, 13, 14]. Immunotherapy improves sleep symptoms, sleep architecture, RBD, and seizures. Some patients may develop insomnia after steroid therapy, and 20–60% remain with poor perceived sleep quality for several months thereafter, even after steroid removal. VPSG studies with nocturnal EEG demonstrate subclinical seizures and FBDS in 30–40% of the patients during the recovery phase that may be a marker of disease activity indicating the need to intensify the immunotherapy [1, 13, 14].

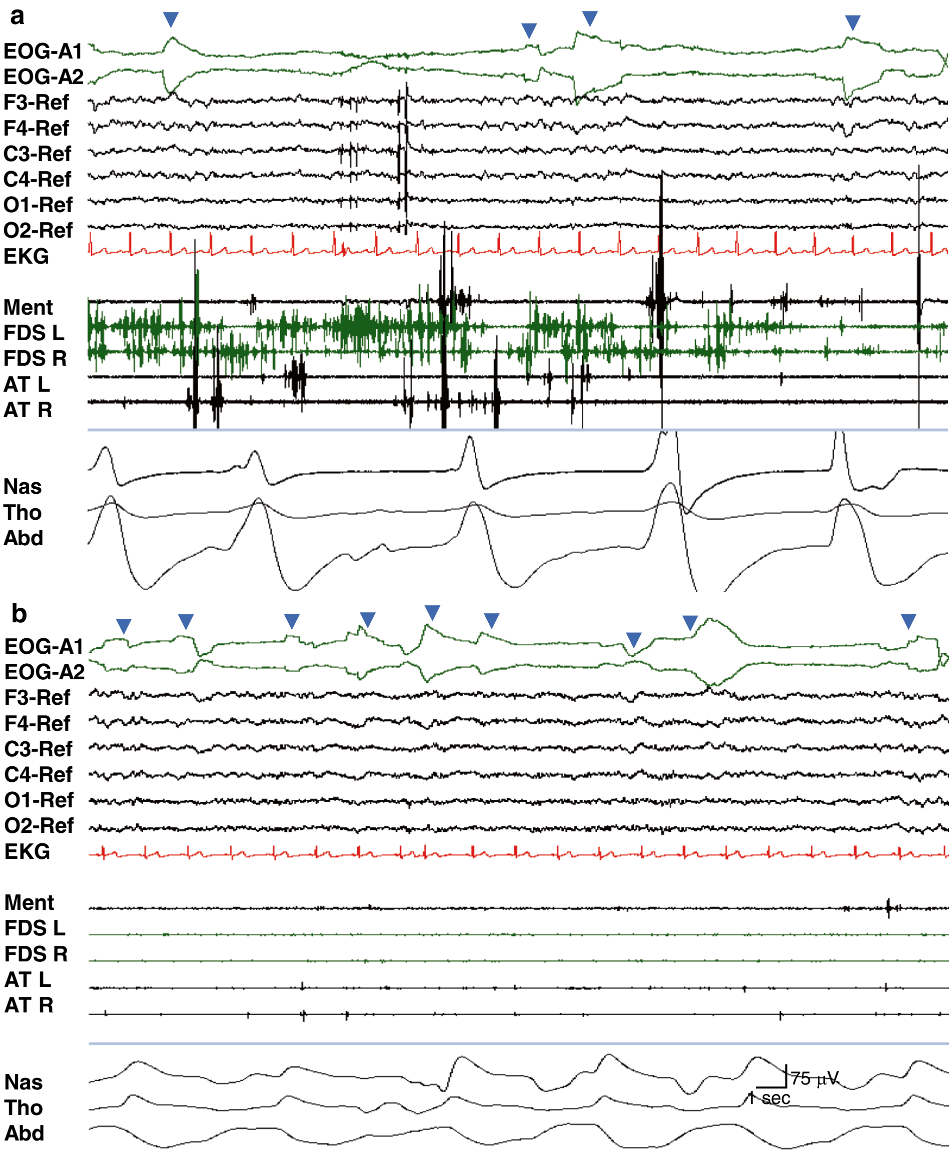

Fig. 90.1 REM sleep behavior disorder in encephalitis associated with LGI1 antibodies. (**a**) REM sleep with excessive tonic and phasic EMG activity in the mentalis and limb muscles typical of a REM sleep behavior disorder in a patient with LGI1 encephalitis. Note the rapid eye moments in the EOG (arrows) and the EEG with mixed frequencies typical of REM sleep. (**b**) Three months after immunotherapy (steroids and intravenous immunoglobulins), REM sleep was normalized with preserved muscle atonia. *EOG* electrooculogram, *EKG* electrocardiogram, *Ment* electromyography (EMG) of mentalis muscle, *FDS* EMG of flexor digitorum superficialis muscle left (L) and right (R), *AT* EMG of anterior tibialis left (L) and right (R), *Nas* nasal airflow, *Tho* thoracic respiratory movement, *Abd* abdominal respiratory movement. (All pictures represent a 30-second epoch. Ref: EEG electrodes were referenced to both ears)

Morvan Syndrome

Morvan's syndrome is characterized by the combination of symptoms of nervous system hyperexcitability, including central (insomnia, encephalopathy, psychosis), peripheral (neuromyotonia), and autonomic (hyperhidrosis, hyperthermia, cardiovascular instability, urinary and sexual dysfunction) dysfunction. About 80% of patients with Morvan syndrome harbor Caspr2 antibodies (also associated with isolated neuromyotonia, limbic encephalitis, or cerebellar symptoms), sometimes with concurrent LGI1 antibodies. Around 50% of patients with Morvan syndrome have an underlying thymoma [1, 2, 15, 16].

Severe insomnia is one of the core symptoms of Morvan syndrome and affects up to 90% of patients. The inability to sleep is accompanied by a severe 24-h motor hyperactivation and profuse perspiration, a complex state that has been termed *agrypnia excitata*, for its similarities with fatal insomnia. In this state, patients often have hallucinatory or dream-enactment behaviors where they represent daily-life activities (e.g., eating, doing job-related tasks, combing the hair, conversing), referred to as *oneiric stupor*. VPSG shows extremely reduced sleep efficiency and short periods of sleep consist of theta activity without sleep spindles, K complex and delta slow waves, with brief intrusions of REM sleep and episodes *oneiric stupor* [1, 15, 17].

Anti-IgLON5 Disease

This neurological disorder is associated with antibodies against IgLON5, a cell adhesion protein in the neuronal surface of unknown function, and affects individuals in the 50s or older, with an insidious onset and slow progression.

There is no association with cancer or autoimmune disorders. Anti-IgLON5 disease is clinically characterized by a prominent and distinctive sleep disorder that associates with additional neurological symptoms, including bulbar dysfunction (e.g., dysphagia, vocal cord palsy, or respiratory failure), gait instability, movement disorders (e.g., chorea, craniofacial dyskinesias), and less frequently cognitive decline, gaze palsy, mild dysautonomia, stiffness, spasms, or fasciculations. Brain MRI and CSF analysis are usually normal. Neuropathological examination in some patients with anti-IgLON5 disease showed neuronal loss and deposits of tau protein in the hypothalamus and tegmentum of the brainstem, suggesting an underlying neurodegenerative process [18]. IgLON5 antibodies, however, are pathogenic as they produce an irreversible internalization of the IgLON5 protein and subsequent abnormalities in the neuronal cytoskeleton. A strong association with the HLA haplotype DRB1*1001 and DQB1*0501 (present in 60–80% of the patients) further supports an immunological basis for this disorder, where autoimmunity and degeneration seem to have an interplay.

Immunotherapy (e.g., intravenous steroids, plasma exchange, or rituximab) is worth being tried as some patients can improve, and there is a significant morbidity and mortality, with sudden death occurring in 20–40% of the patients [18, 19].

Sleep problems occur in 90% of the patients with anti-IgLON5 disease and are clinically characterized by abnormal sleep related vocalizations, movements and behaviors, sleep apneas, insomnia, and mild to moderate EDS [1, 18, 20]. VPSG shows a complex parasomnia involving both NREM and REM sleep, with frequent OSA and stridor. NREM sleep initiation is abnormal and occurs as undifferentiated NREM sleep (characterized by diffuse irregular theta activity without vertex waves, K complexes, sleep spindles, or delta slowing) or poorly structured N2 NREM sleep (with sparse but identifiable spindles and K complexes) associated with vocalizations (e.g., murmuring, whispering, groaning, or talking) and purposeful-looking movements (e.g., resembling an activity of daily life, such as eating, manipulating wires, or picking up objects) (Fig. 90.2). REM sleep is characterized by loss of muscle atonia with limb and body jerks typical of RBD. Despite these NREM and REM sleep abnormalities, and in contrast to Morvan syndrome, there are periods of normal NREM sleep with frequent OSA and stridor that can be treated with continuous positive air pressure or tracheostomy [18, 20].

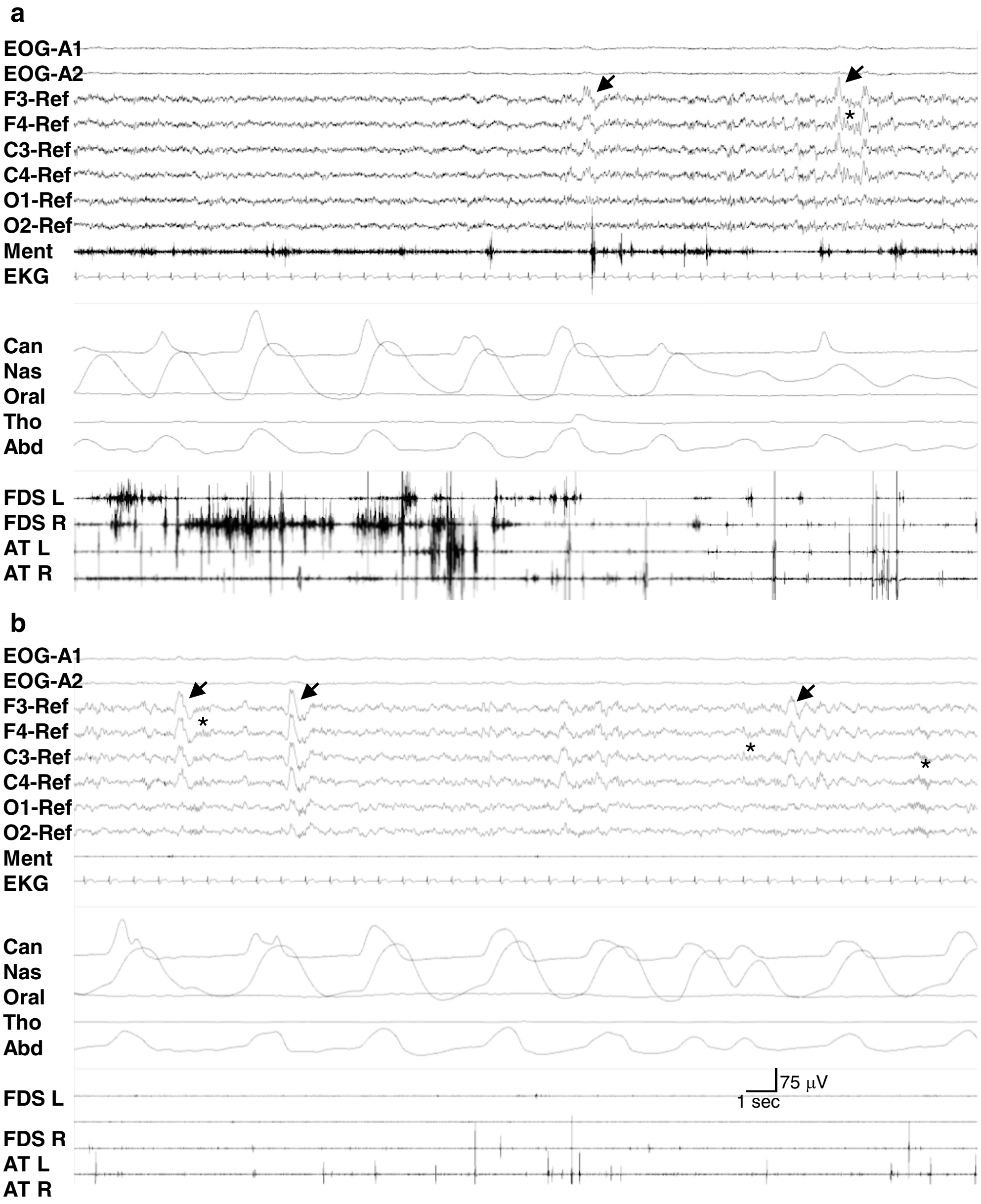

Fig. 90.2 NREM parasomnia in anti-IgLON5 disease. (**a**) Poorly structured N2 NREM sleep with sparse K complexes (arrows) and sleep spindles (asterisks) in a patient with anti-IgLON5 disease associated with frequent muscle activity in EMG of the limbs that correlates with vocalizations and simple and quasi-purposeful movements. (**b**) Period of normal stage N2 with well-formed sleep spindles (asterisks) and K complexes (arrows), later in the night in the same patient. Note the absence of motor activation in the EMG channels. *EOG* electrooculogram, *Ment* electromyography (EMG) of mentalis muscle, *EKG* electrocardiogram, *Can* airflow measured with a pressure transducer, *Nas* nasal airflow, *Or* oral airflow, *Tho* thoracic respiratory movement, *Abd* abdominal respiratory movement, *FDS* EMG of flexor digitorum superficialis muscle left (L) and right (R), *AT* EMG of anterior tibialis left (L) and right (R). (All pictures represent a 30-second epoch. Ref: EEG electrodes were referenced to both ears)

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Autoimmune Stiff-Person Syndromes

91

Sara Llufriu

Abstract

Stiff-person spectrum disorder (SPSD) is a rare autoimmune condition encompassing various syndromes characterized by central nervous system hyperexcitability. This disorder manifests as progressive stiffness, spasms, and an exaggerated startle response to different stimuli, typically unfolding in a subacute manner. Several autoantibodies have been associated with SPSD, but the most common is the presence of high titers of anti-glutamic acid decarboxylase (anti-GAD). Accurate diagnosis of these syndromes demands a high degree of suspicion, necessitating a comprehensive therapeutic approach involving both antispasmodic medications and immunomodulatory treatments.

Keywords

Stiff-person spectrum disorder · Progressive encephalomyelitis with rigidity and myoclonus · Rigidity · Stiffness · Hyperexcitability · GAD antibody

Description of the Disease

Stiff-person syndrome (SPS), initially documented in 1956 [1], is an uncommon autoimmune disorder characterized by central nervous system hyperexcitability. This manifests as fluctuating limb and truncal muscle stiffness, painful spasms, and exaggerated startle responses [1–10]. The disorder also involves partial or segmental forms, such as the stiff-limb syndrome (SLS), in 12–30%, the progressive encephalomyelitis with rigidity and myoclonus (PERM), and atypical and overlapping syndromes (5–10%) presenting as cerebellar ataxia, epilepsy, brainstem disorders, or myelopathies. All these forms are collectively termed stiff-person spectrum disorder (SPSD) [4, 7, 10].

The SPSD predominantly manifests in women, except for PERM in which most patients are men, and symptom onset is usually acute or subacute. The predominant symptom, rigidity, evolves progressively and affects more commonly the trunk, with fixed spinal deformities in some patients due to longstanding stiffness [1–10]. Lower extremities and proximal limb segments are more commonly affected than upper extremities. Spasms are stimulus-sensitive and initially occur in paroxysms, with fluctuations in frequency, intensity, and duration, but can become continuous as the disease progresses [6, 9]. Jerky muscle contractions may precede myoclonic spasms. Tendon reflexes are characteristically exaggerated, although there is no clonus, and plantar responses are flexor. Exaggerated startle responses, abnormally heightened exteroceptive reflexes, and disinhibition of the brainstem can occur. Patients can show oculomotor disturbances and, in some cases, autonomic dysfunction (Table 91.1).

SPSD is associated with diabetes mellitus in up to 35% of patients and with other autoimmune disorders, including thyroid disorders, pernicious anemia, vitiligo, celiac, and rheumatologic diseases [7]. In 5%, it is a paraneoplastic manifestation [7, 10].

The clinical characteristics, along with the presence of autoantibodies and electrophysiological findings (Table 91.2), are part of the diagnostic criteria [4]. Several antibodies have been associated with SPS, and different neurological manifestations are linked to specific antibody serologies [4, 7, 10, 11] (Table 91.3). The glutamic acid decarboxylase 65 (GAD65) is by far the most common antigen. Other antibodies against the α1-subunit of the glycine receptor (GlyR), amphiphysin, gephyrin, dipeptidyl peptidase-like protein 6 (DPPX), and γ-aminobutyric acid-A (GABA-A) receptor (GABAaR) have been related to SPSD [7, 10, 11].

Treatment is based on a combination of symptomatic drugs and immunotherapy [6, 12].

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Symptoms and Signs [2, 5, 7, 8, 13]

See Table 91.1.

Table 91.1 Symptoms and signs of the stiff-person spectrum disorder

Stiff-person syndrome	
Symptoms	Signs
Progressive muscle rigidity, usually starting in the proximal extremities and extending to the trunk (68%)	Co-contraction of agonists and antagonist muscles
Facial muscle stiffness (28%)	Hyperlordotic spine with limited flexibility
Gait dysfunction and falls. Phobia to falls (10%)	Exaggerated tendon reflexes
Stimulus-sensitive spasms (96%)	Electromyography with continuous activity of motor unit firing at rest
Exaggerated startle responses	Autonomic dysfunction: Paroxysmal autonomic sympathetic hyperactivity, during painful muscle spasms
Diaphoresis, agitation, hypertension, tachycardia	Spasms of the diaphragm and thoracic paraspinal and intercostal muscles
Apneic episodes	Oculomotor disturbances
Stiff-limb syndrome	
Stiffness in a single limb	Rigidity is more frequently present in the upper extremities and proximal segments
Progressive encephalomyelitis with rigidity and myoclonus	
Relapsing-remitting symptoms. Rigidity and spasms	Brainstem dysfunction
Myoclonic jerks	Prominent dysautonomia
Instability	Cerebellar ataxia
Hyperekplexia (pronounced startle response)	Altered level of consciousness
Dysphagia	Transient oculomotor manifestations
	Abnormal lower motor neuron findings
Cerebellar ataxia (overlapping with SPS symptoms)	
Instability	Gait ataxia, limb ataxia
Dysarthria	Nystagmus. Oculomotor dysfunction
SPS with epilepsy	
Seizures. Musicogenic Reflex seizures	Temporal lobe epilepsy

Electrophysiological Findings [2, 6, 14]

See Table 91.2.

Table 91.2 Main electrophysiological findings

Findings	Frequency
Continuous motor unit activity in the thoracolumbar paraspinal and rectus abdominis muscles, as well as muscles in the proximal limbs. Co-contraction of agonist and antagonist muscles. They decrease or disappear during sleep, anesthesia, or under benzodiazepines	Abnormality in the trunk: 100% in SPS, and only in 31% of the SLS Abnormality in a limb: 50% in SPS and 100% in SLS
Decrease in central nervous system inhibitory mechanisms: Stereotyped-motor response to peripheral-nerve stimulation "spasmodic reflex myoclonus" Exaggerated response to exteroceptive stimuli	66%

Table 91.3 Auto-antibodies associated with the stiff-person spectrum disorder

Antibody	Percentage	Clinical characteristics
Anti-GAD 65: High titers (>1000 U/ml)	70–85% of classic SPS	Classic SPS or overlapping syndromes. Higher systemic autoimmunity
Anti-GlyR	10–18% of SPS	SPS-plus/PERM. Better outcome
Anti-Amphiphysin	<5%	More frequent neck and upper limb stiffness. Can be associated with cancer
Anti-Gephyrin	Case reports	
Anti-DPPX	3%	
Anti-GABAaR	3%	Intermediate syndrome distribution. Seizures, limbic encephalitis
Negative for antibodies	33%	

GAD 65 glutamic acid decarboxylase 65, *GlyR* α1 subunit of the glycine receptor, *DPPX* dipeptidyl peptidase-like protein 6, *GABAaR* γ-aminobutyric acid-A receptor

Associated Antibodies [3, 5–7]

The detection of anti-GAD antibodies only in serum and at low titers should be interpreted with caution. The underlying mechanism (e.g., presence and type of antibodies) but not the type of syndrome seems to be an independent predictor of the outcome [7].

Amphiphysin-antibodies are an important marker of paraneoplastic SPSD, mostly related to breast or small cell lung cancer. GlyR-antibodies can be paraneoplastic in approximately 10% of the cases, where the underlying tumors are thymomas, lymphomas, small cell lung cancer, and breast cancer (Table 91.3) [11].

Diagnosis

The diagnostic criteria combine clinical characteristics, electromyographic findings, antibody testing, and treatment response.

Dalakas' 2009 diagnostic criteria [4]:

Major Criteria

(a) Stiffness of the axial muscles, especially abdominal and thoracolumbar paraspinals, leading to hyperlordosis.
(b) Superimposed painful spasms triggered by anxiety, tactile, or auditory stimuli.

(c) Electromyographic evidence of continuous motor unit activity of agonist and antagonist muscles.
(d) Absence of an alternative diagnosis.

Minor Criteria

- Positive anti-GAD65 (or antiamphiphysin) antibodies in serum, assessed by immunocytochemistry, Western blot, or radioimmunoassay.
- Clinical response to benzodiazepines.

New proposed diagnostic criteria have been published in 2023, although they need to be validated in larger cohorts [15]:

1. Clinical—symptoms (1 of 2):
    (a) Stiffness (axial regions, limbs, or both).
    (b) Episodic spasms (axial regions, limbs, or both) triggered by noises, tactile stimuli, emotional stress
2. Clinical—signs during symptomatic phase of illness (1 of 3).
    (a) Increased muscle tone (axial or limb).
    (b) Exaggerated lumbar lordosis.
    (c) Concurrent stiffness of lumbar paraspinal and abdominal muscles.
3. Serological findings (1 of 3).
    (a) High-titer GAD65-IgG in the serum (≥20 nmol/L by radioimmunoprecipitation assay or 10,000 IU/mL by ELISA) or any positive titer in CSF.
    (b) Glycine-R-IgG in serum and/or CSF by live cell binding assay.
    (c) Amphiphysin-IgG in serum and/or CSF by immunohistochemistry and antigen-specific assay as confirmation.
4. Electrophysiological studies (1 of 3).
    (a) Inability to relax paraspinal muscles in needle EMG.
    (b) Exaggerated acoustic or exteroceptive responses by surface EMG.
    (c) Co-contraction of agonist/antagonist muscles by EMG.
5. Exclusion of alternative diagnosis.

Definite: All (1–5). Probable: At least one of #1 or #2 AND #3 AND #5 (seropositive). OR #1, #2, #4, and #5 (seronegative).

The sensitivity of these criteria was 100% and the specificity was 89% in the studied cohort. The benefits of the revisions are that new antibodies are considered as well as the titers of GAD, improving the sensitivity and specificity in the diagnosis.

Treatment

The best therapeutic approach is the combination of symptomatic treatment and immunotherapy. Symptoms improvement can be achieved with gamma-aminobutyric acid-enhancing antispasmodic drugs, such as baclofen, tizanidine, benzodiazepines, and gabapentin. Most patients experience a symptomatic benefit with these medications, although it is common that higher doses are progressively required leading to intolerable side effects [6, 12].

Immunotherapy efficacy has been proved in a randomized crossover trial in patients with SPS who received intravenous immunoglobulin (IVIg) for 3 months [16]. A marked and long-lasting improvement in muscle spasms, mobility, frequency of falls, and activities of daily living and reduction of anti-GAD titers was observed with IVIg. In practice, IVIg is given in monthly intervals for 3–6 months and then a reevaluation of stopping treatment, prolonging infusion frequency or decreasing monthly dose should be individualized [12]. If the benefit of IVIg at 3 months is not sufficient or there is a lack of tolerance to the treatment, rituximab should be considered. Plasmapheresis is an option as an adjunct therapy for severe exacerbations [6, 12].

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Part XI

Ocular Autoimmune Diseases

92

Autoimmune Retinopathies

Alfredo Adán

Abstract

Autoimmune retinopathies (ARs) are uncommon ophthalmic disorders in which autoantibodies directed at various retinal components damage the retina causing progressive vision loss. In most cases, an evaluation reveals an underlying malignancy, placing this condition in the category of paraneoplastic retinopathy (PR) syndromes. Paraneoplastic syndromes affecting the visual system are a group of conditions that arise in the systemic malignancy framework. In rare cases, no such malignancy is found, and the patients are considered to have a presumed non-paraneoplastic autoimmune retinopathy (npAIR). Diffuse photoreceptor degeneration of both cones and rods is present with or without any inflammation. Symptoms usually present bilaterally and, rarely sequentially, over a period of several weeks or months before the underlying malignancy is diagnosed. The diagnosis is made on a high index of suspicion based on the clinical findings.

Keywords

Autoimmune retinopathy · Cancer-associated retinopathy · Melanoma associated retinopathy

Autoimmune retinopathies (ARs) are uncommon ophthalmic disorders in which autoantibodies directed at various retinal components damage the retina causing progressive vision loss. In most cases, an evaluation reveals an underlying malignancy, placing this condition in the category of paraneoplastic retinopathy syndromes (PR).

Paraneoplastic syndromes (PNS) have certain distinguishing characteristics which include thew following: (a) diseased or damaged tissue from the primary neoplasm is far situated; (b) syndrome is not a consequence of primary tumor or primary tumor metastases; (c) a variable temporal relationship that exists between the onset of paraneoplastic syndrome and the diagnosis of the primary tumor; and (d) several paraneoplastic syndromes may be associated with one neoplasm type.

The most frequent specific forms of PR that have been identified include cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), bilateral diffuse uveal melanocytic proliferation (BDMUP), and paraneoplastic vitelliform maculopathy. In rare cases, no such malignancy is found, and the patients are considered to have a presumed non-paraneoplastic autoimmune retinopathy (npAIR).

Epidemiology

In general, PR and ARs are uncommon disorders; their exact prevalence is unknown. Its incidence is equal among women and men, except in MAR where men are more commonly affected [1]. It usually affects older adults. When the retinopathy is associated with cancer, the most common disorders are small-cell lung cancer, gynecological and breast cancer, melanoma, lymphoma, pancreatic, prostate, bladder, laryngeal, or colon cancer [2, 3]. Cancer-associated retinopathies are the most common type of paraneoplastic syndrome seen [4].

Pathologic Features

Diffuse photoreceptor degeneration of both cones and rods is present with or without any inflammation [5]. Scattered melanophages in the outer retina can also occasionally be seen. Ganglion cells in the inner retina, the optic nerve, and the

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geniculocalcarine pathway are all spared. Ganglion cell trans-synaptic atrophy, a marked decrease of bipolar neurons in the inner nuclear layer with normal photoreceptor cells in the outer nuclear layer, can be seen in MAR [6].

Cross-reactivity between cancerous and retinal proteins is responsible for initiating the immune-mediated cascade of events that ultimately leads to photoreceptor degeneration. A variety of antiretinal antibodies have been identified in patients with autoimmune retinopathy, including antibodies to recovering, α-enolase and transductine-α, but seronegative disease is also common. The first and most commonly identified antibody in patients with CAR is directed toward recoverin, a 23-kDa retinal protein that some tumor cells also express [7]. In addition to recoverin, the second most common autoimmune retinal antibody is enolase (46-kDa), followed by a 45-kDa and a 60-kDa protein [8]. Patients with MAR have immunoglobulin G (IgG) autoantibodies that react with human rod bipolar cells [9]. Antibodies directed against the 35-kDa retinal Müller cell layer have been found in some patients with ARs [10]. The presence of anti-recovering antibody is not specific for the diagnosis of CAR. Antibodies against recoverin and other retinal antigens of different molecular weights have been found in a wide spectrum of autoimmune retinopathies, even in retinal degenerative diseases, such as retinitis pigmentosa [11].

Clinical Manifestation (Table 92.1)

Symptoms in both PR and AR are similar. Signs and symptoms can vary depending on the retinal elements that are affected. CAR affects both rods and cones, MAR affects only rods, and AR affects Müller cells [12]. Symptoms usually present bilaterally, and rarely sequentially, over a period of several weeks or months before the underlying malignancy is diagnosed [8]. MAR commonly presents after the melanoma is diagnosed, often at the stage of metastases [1].

Individuals with cone dysfunction have photosensitivity, prolonged glared after light exposure (hemeralopia), reduced visual acuity, and loss of color vision. Individuals with rod dysfunction have difficulty seeing in dim illumination (nyctalopia), prolonged dark adaptation, and peripheral field loss. In either case, positive visual phenomena are often prominent, including flashing lights, flickering, smoky or swirling vision, and other entoptic symptoms. Some patients report transient dimming of vision, which may be mistaken for retinovascular disease. They may even report that their vision is better if they wear dark sunglasses [13].

Table 92.1 Symptoms and signs more commonly associated with cancer-associated retinopathies and autoimmune retinopathies

Symptoms	Signs
Reduced vision acuity	Fundus finding normal at presentation
Loss of color vision	Attenuation of the arterioles
Photopsia	Mottling and thinning of the RPE
Prolonged glare	Vitreous cells
Nyctalopia	Periphlebitis
Floaters	
Flickering and smoky vision	
Peripheral field loss	

Examination findings are variable. Patients with CAR usually have prominent involvement of central vision, resulting in markedly decreased visual acuity, loss of color vision, and central scotomas. In some cases, visual field testing shows paracentral scotomas that progress to classic ring scotomas. Photostress recovery times are typically prolonged. In contrast, patients with MAR often have near-normal visual acuity, color vision, and central visual fields, at least at presentation. Peripheral or mid-peripheral field loss can usually be demonstrated [6, 14].

Fundus findings at presentation are often normal. However, characteristic changes occur over time and include attenuation of the arterioles, with thinning and mottling of the retinal pigment epithelium [15]. In occasional cases of CAR or MAR, vitreous cells, arteriolar sheathing, and periphlebitis may be present, particularly late in the course of the disease.

Fluorescein angiography is often performed to exclude other entities as potential causes of vision loss. Findings are usually normal, but in occasional cases, fluorescein angiography may demonstrate mild peripheral vascular leakage consistent with vasculitis.

The findings from full-field (Ganzfeld) ERG are almost always abnormal; specific findings depend on the predominance of cone versus rod dysfunction. Patients with CAR usually have absent cone responses. Findings in MAR include a markedly reduced or absent dark-adapted b wave, which indicates bipolar and Müller cell dysfunction. Multifocal ERG may be useful in select cases in which visual field loss is localized [16]. In addition, some authors have used multifocal ERG to quantify the loss of electrical activity and to correlate this finding with results of Goldmann perimetry [8].

Diagnosis (Tables 92.2 and 92.3)

The diagnosis is made on a high index of suspicion based on the clinical findings. Early in the course of the ophthalmic diseases, findings on retinal examination may be normal, which makes diagnosis difficult. The initial workup includes a full assessment of the patient's visual function, including color vision and visual field testing. Goldmann perimetry is preferred because it readily tests the peripheral field. Full-field ERG is crucial for localizing the disease

Table 92.2 Antigen proteins in autoimmune retinopathies

Recoverin 23 kDa (the most common in CAR)
Enolase 46 kDa
45 kDa
60 kDa
35 kDa (in some patients with AR)
IgG (patients with MAR)

Table 92.3 Frequency of malignancies associated with cancer-associated retinopathy

Small-cell lung cancer	53%
Non-small-cell lung cancer	11%
Endometrial	10%
Cervical	7%
Breast	6%
Ovarian	5%
Prostate	4%
Pancreatic	4%

process to the retina and for further defining the retinal layers involved [17].

A definitive diagnosis of CAR or MAR requires the demonstration of antiretinal antibodies. Results of such laboratory testing are not always definitive. On occasion, individuals without clinical evidence of retinopathy have these antibodies, and, in some cases of presumed CAR, the antibodies cannot be identified with current techniques.

In any patient with suspected CAR and without a known malignancy, a chest radiograph should be obtained. If the result is normal, a CT scan of the chest is appropriate. Additional imaging studies for a possible primary neoplasm include CT of the abdomen and pelvis, mammography (for women), and total body positron emission tomography (PET) [15].

Differential Diagnosis

Acute or subacute unilateral or bilateral vision loss with a normal-appearing fundus suggests the possibility of retrobulbar optic neuropathy. Specific entities to consider include compressive orbital and intracranial lesions, demyelinating diseases, ischemia, toxicity, and hereditary disorders. In the ideal case, the clinical findings are sufficiently distinctive to distinguish optic nerve disease from retinal disease and therefore obviate extensive neurological testing.

Hemeralopia or nyctalopia, positive visual phenomena, prolonged photostress times, and ring scotomas all suggest the possibility of retinal disease, even in the absence of funduscopic abnormalities, and prompt electrophysiological studies.

Patients with cancer-associated cone dysfunction have bilateral central vision loss with poor color vision and central scotomas. These findings are also compatible with toxic-nutritional optic neuropathy or hereditary optic neuropathy. Multifocal-ERG should be effective for distinguishing optic neuropathy from maculopathy in these patients.

Metastatic disease as the cause of vision loss should include contrast-enhanced MRI of the head and orbits and lumbar puncture for cytological examination. It may be due to infiltration of cancerous cells around the optic nerve. Some chemotherapeutic agents, such as vincristine and carmustine, can cause optic neuropathy. Patients who have received cranial radiation are also at risk for vision loss.

Bilateral diffuse uveal melanocytic proliferation is a possibility in cancers originating from the reproductive tract, retroperitoneal zone, or lungs. Patients with this proliferation develop an orange pigment deposit at the level of the RPE, shown as a diffuse pattern with round areas of hyperfluorescence on fluorescein angiography. These patients usually develop nonpigmented tumors of the iris, cataracts, and exudative retinal detachments [18].

Once it is clear that the patient's vision loss is due to photoreceptor dysfunction, the differential diagnosis is narrowed to paraneoplastic syndromes, hereditary photoreceptor degeneration (e.g., cone dystrophy, retinitis pigmentosa), and toxic retinopathy. Patients should be questioned regarding the use of potential retinal toxins, such as chloroquine or hydroxychloroquine.

Cases of acute zonal occult outer retinopathy (AZOOR) are occasionally confused with PR. The no-seeing areas are sharply demarcated from the surrounding areas, the involvement is usually unilateral, and the disease has a predilection for the peripapillary area. Full-field ERG is generally normal, in distinction from PR in which ERG findings are markedly attenuated or flat early in the course of the disease. MERG demonstrates the abnormality well.

Therapy

Treatment of the underlying malignancy, steroid therapy, plasmapheresis, and administration of intravenous immunoglobulin are disappointing over all. Delayed diagnosis and treatment initiation relatively late in the disease course may contribute to the poor visual prognosis. Corticosteroids have been shown to decrease antibody titers in patients with CAR, but they do not reverse vision loss [1]. These results may suggest that if the photoreceptors sustain sufficient damage, visual function is permanently altered. Current research involves the following: methods of blocking antibody-mediated apoptosis by means of changes in intracellular calcium and activation of recovering-specific antitumor cytotoxic T lymphocytes. Another promising therapy involves autologous tumor cells transfected with interleukin-2 genes that are used as a vaccine to generate an immune response against the tumor cells [19].

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Autoimmune Uveitis

93

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Abstract

Autoimmune uveitis (AU) is an important cause of blindness and should be diagnosed as early as possible and efficiently treated in order to avoid it. It can be due to an isolated type of autoimmune reaction against the uveal components or be related to or precede a known systemic autoimmune disease. A diagnosis of a systemic autoimmune disease should be investigated, and the patient's treatment should be tuned in accordance with the other organs involved.

The autoimmune diseases where uveitis is most commonly seen are spondyloarthropathies inflammatory bowel disorders, juvenile idiopathic arthritis, Behcet's disease, and sarcoidosis.

Keywords

Uveitis · Ocular inflammation · Spondyloarthropathies · Behcet's disease

Definition

Uveitis describes a group of conditions characterized by intraocular inflammation. The term uveitis technically describes inflammation of the uvea which comprises the iris, ciliary body, and choroid. As intraocular inflammation can affect surrounding tissues, the clinical term uveitis may include inflammation of the retina (retinitis), optic disc (papillitis), and vitreous (vitritis). Uveitis is a condition with global impact and with direct relevance to health professionals working across many sectors and specialties. The suspicion of uveitis requires a prompt referral to an ophthalmologist, combined with an urgent diagnostic workup in order to treat and control the inflammatory process.

It may be the first presentation of serious systemic disease and be a vital warning sign that allows early diagnosis and medical intervention.

Clinical Picture and Classification (Table 93.1)

Anterior uveitis (AU) is by far the most common type and can be manifested as iritis, which affects only the iris and iridocyclitis, which involves the ciliary body in addition to the iris. Intermediary uveitis is also known as vitritis and is characterized by the infiltration of inflammatory cells in the vitreous cavity, sometimes with the involvement of the pars plana. The posterior uveitis can be of three types: choroiditis, retinochoroiditis, and chorioretinitis, also related to the involved area. Finally, there is the type called panuveitis, which is characterized by the diffuse involvement of the whole uveal tract.

At presentation, eye redness is the major symptom, with the exemption of the juvenile idiopathic oligoarticular or psoriatic arthritis and is often accompanied by injected con-

Table 93.1 Noninfectious systemic disorders related to uveitis

Seronegative spondyloarthropathies
Ankylosing spondylitis
Psoriatic arthritis
Reactive arthritis
Inflammatory bowel diseases
Juvenile idiopathic arthritis
Behçet disease
Vogt–Koyanagi–Harada syndrome
Sarcoidosis
Infectious origin
Herpes
Syphilis
Tuberculosis

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junctiva, local pain, photophobia, and decreased visual acuity (blurred vision). Patients may also complain of seeing dark, floating spots along the visual field. The clinical course of the anterior uveitis can be manifested as an acute form, with sudden onset, characterized by a single episode that may last for 2 to 3 months that improves with prompt proper treatment, or may persist as a recurrent or chronic form. An AU that persists for more than 3 months is classified as chronic. The AU onset is usually insidious but may also have a recurrent course. The major findings are dilation of the ciliary vessels, presence of inflammatory cells in the anterior chamber, and keratic precipitates (KPs) on the corneal posterior surface. These findings can be divided as granulomatous type, where the KP is of a "mutton-fat" type or nongranulomatous, where the KPs are thinner. In accordance to the number of inflammatory cells found, the ophthalmologists refer to mild or severe forms. Complementary tests are crucial in order to differentiate the AU from those of infectious origin.

Uveitis can be classified according to:

The anatomical parts of the eye affected by the disease and the underlying etiological cause. In relation to the course of uveitis, it comprises acute (i.e., sudden onset and limited duration), recurrent (repeated episodes separated by periods of inactivity off treatment of greater than 3 months in duration), and chronic (persists and relapses in less than 3 months after discontinuing treatment).

Most noninfectious causes appear to be autoimmune or autoinflammatory in nature and may be associated with systemic conditions, characterized by dysregulation of the immune system or inflammasome (a multiprotein sensor that activates innate immunity after detecting pathogens). Associations include ankylosing spondylitis (AS), for whom uveitis is the most common extra-articular complication, arising in up to 50% of patients [1]. Similarly, uveitis is a significant extra-articular manifestation of inflammatory bowel disease (IBD) and reactive arthritis, although less commonly than in AS [2].

In around one-third of uveitis, no associated systemic disease or other precipitant is identified. Such uveitis is termed "idiopathic," although there is good evidence for it having an autoimmune/autoinflammatory etiology.

Seronegative Spondyloarthropathies

Included in this group are a series of diseases that have in common the involvement of the axial skeleton with negative rheumatoid factor (RF) and no other specific serologic marker. The most prevalent disease of this group is ankylosing spondylitis (AS). Other diseases in this group are psoriatic arthritis, reactive arthritis, and arthritis related to the inflammatory bowel diseases (Crohn's disease and ulcerative colitis). There is a strong relationship with the presence of the class I antigen HLA-B27.

AS affects more commonly young Caucasian males and more than 90% have the HLA-B27. In addition to low-back pain due to sacroiliitis, there is a high frequency of periarticular pain, manifested as oligoarthritis related to enthesitis. The radiographic findings of sacroiliitis may take years to appear, and this may postpone the diagnosis in years. Of the extra-articular manifestations, those in the skin and the eyes are the most common ones. The most frequent ocular manifestation of AS is a non-granulomatous, unilateral anterior uveitis, characterized by acute recurrent attacks of iridocyclitis and sometimes pars planitis. More rarely, there may be a chronic evolutionary course with the development of secondary glaucoma, complicated cataract, and keratopathies. These complications may hamper the visual function. Uveitis may precede the diagnosis of AS in years. In reactive arthritis and psoriatic arthritis, the most common ocular manifestation is conjunctivitis, being bilateral in the first [3].

The laboratory tests are nonspecific and related to the chronic inflammatory process. Acute phase reactants, such as C-reactive protein, may be elevated in the plasma, as well as the level of circulating IgA. The HLA-B27 detection is not necessary for diagnosis.

Local treatment for anterior uveitis in these patients is with mydriatic and corticosteroid eye drops. In refractory cases, subtenonian infiltration or intravitreal injection with corticosteroids may be attempted.

Inflammatory Bowel Diseases

Ocular manifestations are found in about 2.5% of the patients with Crohn's disease and 5–12% of those with ulcerative colitis. The lesions are in general non-granulomatous, involving bilaterally the anterior uvea, and tend to be recurrent. Chronic posterior uveitis has also been reported in patients with inflammatory bowel diseases. The treatment of the ocular lesions in patients with inflammatory bowel diseases consists of using local or systemic corticosteroids.

Juvenile Idiopathic Arthritis (JIA)

JIA is diagnosed when there is persistent arthritis for more than 6 weeks in persons less than 16 years old, once other causes of arthritis are ruled out. JIA is classified according to the type of articular involvement. The systemic type (Still's disease) is the most severe form and the least frequent, encompassing around 10% of the cases, and can be found equally in both genders; they present an intermittent fever with skin rash with symmetric arthritis and no RF.

The polyarticular form accounts for 30–40% of the cases, and five or more joints are involved and most of the cases do not display RF [4]. The RF-positive polyarticular subtype is a distinct entity, and it has a similar course as rheumatoid arthritis, it presents only 5% of the JIA cases. The oligoarticular form affects 40–50% of the cases of JIA, and less than five joints are involved; around 50% of the patients are positive for antinuclear antibodies. Another subtype resembles the adult spondyloarthropathies; they are called juvenile idiopathic enthesitis-related arthritis, and the presence of sacroiliitis is not required for the diagnosis. In the pediatric cohort, enthesitis and peripheral asymmetric arthritis of the lower limb are mostly dominant [5].

Uveitis is rare in the systemic form and occurs around 10% in the polyarticular RF-negative form. However, it is detected most frequently in the oligoarticular form (around 20% of the cases). A chronic bilateral iridocyclitis due to non-granulomatous anterior uveitis without pain and redness of the involved eye is the most typical finding. In a lot of cases, at the time of the diagnosis, complications like cataract or band keratopathy are present. Uveitis at the time of diagnosis of JIA or before the diagnosis of JIA is a bad prognostic factor. Uveitis in these patients is mostly painless, and that is the justification for the suggested periodic eye exam in patients with JIA according the recommendations. The ocular treatment includes local corticosteroids and mydriatics. For the cases of chronic iridocyclitis, systemic corticosteroids as bridging agent with an immunosuppressor like methotrexate are indicated, and in severe cases, the addition of tumor necrosis factor (TNF)-blocking agents [6] is indicated.

Behçet Disease

Behçet uveitis is commonly considered a panuveitis that can result in severe visual impairment unless it's not managed properly. Behçet's disease is important because of the severity of its ocular manifestations and their treatment [7, 8]. The posterior ocular involvement of Behçet's uveitis is mainly responsible for the severity of visual prognosis. Vitritis, retinal vasculitis, retinitis, and papillitis are the hallmark lesions of Behçet posterior and panuveitis. Is possible to detect the onset of uveitis by pearl-like precipitates that appear over the retinal surface and later disappear. Retinal vasculitis of Behçet's uveitis is best demonstrated by fundus fluorescein angiography, revealing widespread perivascular leakage that can cover all peripheral retina.

Vascular involvement can occasionally present with occlusive vasculitis that causes vitreal and retinal hemorrhages. The intense posterior ocular inflammation can result in late-stage manifestations like papillary and retinal neovascularization, vascular fibrotic sheathing, epiretinal membrane, and retinal detachment.

The primary treatment options for Behçet's disease and uveitis are corticosteroids, which are either used systemically for posterior and panuveitic inflammation or topically for more limited anterior uveitis. However, since you want to control Behçet's disease for the long term and corticosteroids might have considerable adverse effects, immunosuppressive and immunomodulatory treatment options are usually applied together with or in the absence of systemic corticosteroids. Conventional immunosuppressants like cyclosporine, azathioprine, and methotrexate are frequently used for long-term treatment, whereas increasing evidence emerges in favor of biological agents such as anti-TNF (infliximab, adalimumab) and interferon, demonstrating superior treatment efficacy and tolerability [9].

Vogt–Koyanagi–Harada Syndrome

It is a multisystemic disorder that typically affects pigmented skin individuals. In the Japanese population, where the disease is more prevalent, there is a strong relationship with the presence of HLA-DR4. In addition to the eyes, typical manifestations involve the ears, the skin, and the central nervous system [10]. The characteristic presentation is a severe bilateral diffuse granulomatous uveitis with signs of meningeal irritation, bilateral neuro-sensorial dysacusia, and skin alterations, such as vitiligo, alopecia, and poliosis.

Angiography and ultrasound exams are necessary for the ocular diagnosis. A prodromic period is followed by the uveitis phase that lasts 3–5 days or several weeks. Then, a convalescence phase issues with dyspigmentation of the skin, as well as the uvea and the pigmented retinal epithelium; this phase can last for months or years. Recurrent attacks can happen during the convalescence phase. The anterior uveitis should be promptly treated with local corticosteroids and mydriatics, while the posterior form responds to periocular or intravitreous corticosteroids. As soon as the diagnosis of Vogt–Koyonagi–Harada syndrome is confirmed, systemic high-dose corticosteroids should be started along with a potent immunosuppressor agent [11].

Sarcoidosis

It is a multisystemic granulomatous disease characterized by the deposition of CD4 cells and macrophages in the involved sites. Sarcoidosis occurs in all age groups but is more common in persons between the ages of 20 and 50 years, with a preference for Afro descendants. Cutaneous involvement is common; in the initial phase, there may be pulmonary and hepatic alterations. Of the patients with systemic disease, 27–40% present AU; isolated eye sarcoidosis can also occur [12]. In half of the cases with ocular manifestations, the presentation is an acute and self-limited granulomatous iridocyclitis. The chronic presentation is mostly seen in older patients with pulmonary fibrosis and quiescent systemic disease. Alterations in the vitreous can also be seen, like posterior segment periphlebitis, retinal and choroidal granulomas, and lesions of the optic nerve, in addition to lacrimal glandular and conjunctival involvement. It is important to recognize sarcoidosis as a cause of uveitis, because it imposes a systemic involvement screening as well as a proper therapeutic intervention. Chest CT scan is useful to demonstrate hilar adenomegaly, with or without multifocal parenchymatous nodular lesions. Gallium whole-body scan is used to investigate the hypercaptation in lacrimary glands and orbital area, as well as in salivary glands and lungs; its value is enhanced when combined with the measurement of the serum angiotensin-converting enzyme level [13].

Treatment of Noninfectious Intermediate, Posterior, or Panuveitis

- Systemic treatment is common, with corticosteroids as first-line therapy. In severe inflammation, this may be with pulsed intravenous methylprednisolone or with high-dose oral prednisolone. The numerous side effects of systemic corticosteroids, particularly at high doses, can be reduced through a maintenance dose of less than 7.5 mg/day. A failure to achieve this indicates the need for some alternative or additional treatment, such as the introduction of a second-line immunosuppressant (commonly mycophenolate mofetil, methotrexate, ciclosporin, or tacrolimus) or additional local therapies. The use of biological therapies (commonly adalimumab or infliximab) is effective and is commonly used as a third-line treatment [14–16].
- Local treatment is increasingly common and is usually corticosteroid-based, although nonsteroid drugs are under evaluation. Ozurdex, a dexamethasone implant, may last for up to 6 months and is licensed for the treatment of noninfectious uveitis affecting the posterior segment of the eye. These drugs are effective but have significant rates of elevated intraocular pressure and cataract formation. Despite these limitations, they are very useful, particularly in the treatment of unilateral or asymmetric disease, where they can mitigate the level of systemic immunosuppression required [17].

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94

Vogt-Koyanagi-Harada Disease

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Abstract

Vogt-Koyanagi-Harada disease (VKH) is a multisystem autoimmune disorder affecting pigmented tissues such as the eye, auditory, integumentary, and central nervous systems. Patients are typically females between 20 and 50 years old with no previous history of penetrating ocular trauma. The clinical course of VKH is divided into four phases: prodromal (mimics a viral infection), uveitic (bilateral diffuse uveitis with papillitis and exudative retinal detachment), convalescent (tissue depigmentation), and chronic recurrent (recurrent uveitis and ocular complications). Clinical, laboratory, and experimental data corroborate the autoimmune nature of VKH disease: a CD4+ T cell-mediated immune response directed against self-antigens found on melanocytes in a genetically susceptible individual. HLA-DRB1*0405 is the primary susceptibility allele found in patients with VKH. According to the revised diagnostic criteria, the disease is classified as complete, incomplete, or probable based on the presence of extraocular findings. The diagnosis of VKH is clinical, and differential diagnosis includes sympathetic ophthalmia, sarcoidosis, primary intraocular B-cell lymphoma, posterior scleritis, and uveal effusion syndrome. Treatment is based on initial high-dose oral corticosteroids with a low tapering during a minimum period of 6 months. Systemic immunosuppressants, such as cyclosporine, azathioprine, mycophenolate mofetil, and adalimumab, may be used in refractory or corticosteroid non-tolerant patients. Visual prognosis is usually good under a prompt diagnosis and adequate treatment.

Keywords

Vogt-Koyanagi-Harada · Uveitis · Diagnostic criteria · Ophthalmological findings · Treatment

Introduction

Vogt-Koyanagi-Harada disease (VKH) is a multisystemic granulomatous autoimmune disease affecting pigmented tissues of the eye, the central nervous system, the internal ear, and the skin. Patients with bilateral uveitis associated with poliosis, vitiligo, alopecia, and dysacusia were first described by Vogt in 1906 [1] and then by Koyanagi in 1929 [2]. In 1926, Harada described a case of uveitis with exudative retinal detachment associated with pleocytosis of the cerebral spinal fluid [3].

Pigmented races are more susceptible, with Asians, Hispanics, Native Americans, and Middle Easterners displaying a greater prevalence than Caucasians and individuals of African descent. Women are affected more frequently than men, and there is a clear predominance in the third to fourth decade of life, although children as young as 4 years old with VKH and similar sex predilection have been reported. VKH is more prevalent in Japan, accounting for 10.1% of all uveitis compared to 1–4% in the USA [4] or 2.5% in Brazil [5].

Although the etiology of VKH is not yet fully clarified, several pieces of evidence corroborate the autoimmunity against tyrosinase-like proteins in melanocytes triggered by an unknown factor in a genetically susceptible individual [6]. The prodromic manifestations point to a viral trigger such as herpes family virus (Epstein-Barr virus, cytomegalovirus). Studies have shown an association of HLA-DRB1*0405 and DRB1*0410 with increased susceptibility to VKH [7].

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Classical histopathological findings are a diffuse granulomatous bilateral uveitis. The choroid is remarkably thickened and infiltrated with lymphocytes, macrophages, epithelioid, and giant cells. Another characteristic finding is the Dalen-Fuchs nodules that consisted of macrophages, epithelioid cells, lymphocytes, and altered retinal pigment epithelium cells localized between the Bruch membrane and retinal pigment epithelium [8].

Clinical Manifestations

VKH has four distinct clinical phases: prodromal, uveitic, convalescent, and chronic/recurrent. The prodromal phase manifests with general symptoms, such as fever, nausea, and headache, lasting 3 to 5 days. Subsequently, the uveitic phase starts with ocular symptoms, including photophobia, blurred vision, and ocular pain. Bilateral granulomatous anterior uveitis with mutton fat keratic precipitates, and iris nodules are observed upon eye examination. In addition, diffuse choroiditis associated with exudative retinal detachment and optic disc hyperemia is identified. Swelling of the ciliary body may displace the lens-iris diaphragm forward with consequent shallowing of the anterior chamber, angle narrowing, and an acute increase in intraocular pressure [8, 9].

In the convalescent phase, due to appropriate treatment, the choroiditis and the exudative retinal detachment gradually subside. In this phase, it is observed the typical "sunset glow" fundus (orange-red fundus appearance), multiple scattered, discrete, depigmented retinal pigment epithelial lesions in the mid-periphery of the fundus and retinal pigment epithelial migration, all denoting the profound melanocyte and pigmented tissue aggression. Sugiura sign is the depigmentation of limbus mainly reported by Japanese authors. In this phase, cutaneous depigmentation is observed.

Recurrence or chronicity of the uveitis may occur in 17 to 73% of cases. The recurrence is usually anterior; nevertheless, signs of disease activity in the posterior pole of the eye have been reported, suggesting relentless melanocyte aggression. In the convalescent and chronic phases, ocular complications may be observed, such as glaucoma, cataracts, choroidal neovascular membranes, and retinal/choroidal gliosis. These long-term ocular complications may lead to final low visual acuity [8, 9].

Extraocular manifestations are characteristically observed in convalescent and chronic phases. Dysacusia, tinnitus, high-frequency hearing loss, and vertigo may involve the auditory system. Similarly, the central nervous system can be affected by headache, meningismus, and pleocytosis in the cerebral spine fluid that precedes the ocular involvement by 1–2 weeks. Infrequently, focal neurological signs such as cranial nerve palsies and optic neuritis can occur. Cutaneous manifestations, commonly observed in the convalescent and chronic phases, are vitiligo of the hands, shoulders, breast, back, and face, poliosis, localized hair whitening, and alopecia [8, 9].

The frequencies of the main clinical manifestations and ophthalmological findings [10–13] are summarized in Tables 94.1 and 94.2.

Table 94.1 Clinical manifestations of Vogt-Koyanagi-Harada syndrome

Signs and symptoms	Frequency
Headaches	49–63%
Photophobia	48%
Visual disturbance	31–70%
Tinnitus	21.7–36%
Weakness	21%
Hearing loss	18%
Dysacusis	17–32%
Flu-like symptoms	17%
Nausea	13%
Alopecia	10.9–35.2%
Poliosis	10–36%
Vitiligo	4.7–20%
Neck stiffness	1.6–33%

Rao et al. 2010 [10]; Yang et al. 2018 [11]; Jabs et al. 2021 [12]; Wu et al. 2022 [13]

Table 94.2 Ophthalmologic findings of Vogt-Koyanagi-Harada syndrome

Ophthalmologic findings	Frequency
Nummular chorioretinal scars	46%
Vitreous cells	38–49.4%
Cataract	37–42%
Anterior chamber cells	36–79.5%
Sunset glow fundus	31.8–58%
Exudative retinal detachment	30.2–59.8%
Anterior chamber flare	24–50.6%
Keratic precipitates	22–39%
Choroidal thickening/diffuse choroiditis	20–54.4%
Disc hyperemia/swelling	13–46.5%
Glaucoma	10–33.8%
Dalen-Fuchs nodules/multifocal chorioretinal atrophy	8.5–40.8%
Retinal pigment epithelium clumping/migration	8.5–45%
Subretinal fibrosis	8%
Bilateral recurrent granulomatous anterior uveitis	5.4–53.9%
Sugiura sign	5–85%
Subretinal fluid	4%
Subretinal neovascularization	2%
Bullous detachment	0–6%

Rao et al. 2010 [10]; Yang et al. 2018 [11]; Jabs et al. 2021 [12]; Wu et al. 2022 [13]

Differential Diagnosis

The primary differential diagnosis of VKH disease is sympathetic ophthalmia, which presupposes the existence of previous ocular trauma or surgery. Other conditions that may mimic VKH disease are acute posterior multifocal placoid pigment epitheliopathy (APMPPE), posterior scleritis, sarcoidosis, tuberculosis, intraocular primary lymphoma, metastatic carcinoma, idiopathic uveal effusion syndrome, and other white-dot syndromes and conditions related to diffuse choroiditis [14]. Based on this, a complete history and physical examination followed by blood tests, tuberculin tests, and images should be performed on all patients.

Complementary Tests

The diagnosis of VKH disease is clinical; nevertheless, complementary exams may be helpful in atypical cases. Cerebrospinal fluid (CSF) pleocytosis is observed in 77–79% with a predominance of lymphomonocytes, especially within the first 3 weeks after disease onset [10]. Ultrasonography of the eye reveals low to medium reflective diffuse thickening of the choroid with localized and extensive retinal exudative detachment, differentiating VKH from higher reflectivity of idiopathic uveal effusion and metastatic carcinoma. Fluorescein angiography in the acute phase of the disease typically shows multiple hyperfluorescent pinpoints, corresponding to choroiditis lesions, which coalesce into larger areas corresponding to the exudative retinal detachment [15]. The use of indocyanine green angiography (ICGA) has provided advances in the evaluation of posterior uveitis by allowing more accurate assessments of inflammation in the choroidal compartment. Optical coherence tomography (OCT) is a noninvasive modality that increases the precision of analyzing exudative retinal detachments in acute initial-onset VKH disease. OCT can also reveal early signs of macular complications and indicators of subclinical inflammation, such as macular edema, in chronic VKH. Additionally, it provides a means for closely monitoring lesion remission after treatment. Enhanced depth imaging-OCT (EDI-OCT) is a modern imaging modality that proves valuable in offering insights into choroidal thickness, thereby aiding in the assessment of inflammatory choroidal infiltration [16].

The frequencies of the main findings of complementary tests [10–13] are summarized in Table 94.3.

Table 94.3 Complementary tests in Vogt-Koyanagi-Harada syndrome

Complementary tests	Frequency
FFA finding	
D or M or L or P or choroidal thickening	90%
D or M or L or P	83%
Multifocal leaks (M)	70%
Optic disc staining/hyperfluorescence	64.6–79.8%
Subretinal pooling of dye (P)	56%
Large placoid areas of hyperfluorescence (L)	43%
Choroidal perfusion delay (D)	41%
Early punctate staining and late subretinal dye pooling	26.4–44.2%
D or M or L or P and choroidal thickening	22%
Window defects/moth-eaten fluorescence	5.4–49.9%
OCT finding	
Serous retinal detachment	49.2–63.6%
EDI-OCT finding	
Choroidal thickening	46.5%
ICGA finding	
Hypofluorescent dark dots	44.2–79.7%
B-scan ultrasonography finding	
Retinal detachment	39.4%
Choroidal thickening	20%
Evidence of posterior scleritis or thickening of ocular wall	2.3%
CSF finding	
CSF pleocytosis	77–79.2%

CSF cerebrospinal fluid, *D* choroidal perfusion delay, *EDI* enhanced depth imaging, *FFA* fluorescein fundus angiography, *ICGA* indocyanine green angiography, *L* large placoid areas of hyperfluorescence, *M* multifocal leaks on FA, *OCT* optical coherence tomography, *P* subretinal pooling of dye, *US* ultrasonography

Rao et al. 2010 [10]; Yang et al. 2018 [11]; Jabs et al. 2021 [12]; Wu et al. 2022 [13]

Diagnostic Criteria

In 1980, the American Uveitis Society proposed a diagnostic criterion (AUS) [4] considering those previously suggested by Sugiura [17]. However, these criteria come short in making the diagnosis in the acute phase as two of the four criteria occur only in the chronic phase, namely, chronic bilateral iridocyclitis and cutaneous signs. In an effort to unify concepts and allow the comparison of results from clinical studies from different countries, the International Committee on Nomenclature proposed the Revised Diagnostic Criteria for

VKH disease (RDC) in 2001 [18] (Table 94.4). The RDC subdivides patients into three categories: probable, incomplete, and complete. It encompasses a broader range of patients as the ocular manifestations may be acute or chronic to meet the criteria.

However, despite the RDC presenting better sensitivity and specificity than the AUS and Sugiura criteria and being widely used at present, it also has some significant limitations, such as not allowing for a complete diagnosis without the presence of extraocular manifestations and the need for characteristic changes in the fundus of the eye. It is known that typical fundus changes may not be visible in patients treated early, and the visualization of the fundus of the eye can be compromised by late-stage disease opacities [11]. The corticosteroid therapy may prevent the development of late-stage disease. It can be one of the reasons for the low proportion of patients classified as having complete VKH (12%), according to RDC, found in a study by Rao et al. [10, 12].

In this regard, other criteria have been suggested, such as the Diagnostic Criteria for VKH Disease (DCV), which was studied in a large Chinese population and demonstrated improved sensitivity (94.6% vs. 71.9%) and similar specificity (92.2 vs. 93.9%) to the diagnosis of VKH compared to the RDC [11]. DCV distinguished the initial onset from the late phase of VKH disease, and the extraocular findings were omitted. Studies have shown frequencies between 14.9% and 42.2% of VKH cases with only ocular manifestations [10, 13, 19]. Another advantage of DCV over RDC was incorporating new technologies such as OCT and EDI-OCT. These techniques help in recognizing subtle serous retinal detachment and choroidal thickening. On the other hand, DCV is limited to being developed using retrospective analysis data in a specific Asian population [11].

Table 94.4 Revised diagnostic criteria for VKH

1. No history of penetrating ocular trauma
2. No evidence of other ocular or systemic disease
3. Bilateral ocular disease—either a or b: *a. Early manifestations* i. Diffuse choroiditis manifested as either 1. Focal areas of subretinal fluid or 2. Bullous serous retinal detachments ii. If equivocal fundus findings, then both of the below 1. Fluorescent angiography showing focal delayed choroidal perfusion, pinpoint leakage, pooling within subretinal fluid, and optic nerve staining 2. Ultrasound showed diffuse choroidal thickening without posterior scleritis *b. Late manifestations* i. History suggestive of above, and both ii and iii or multiple from iii ii. Ocular depigmentation 1. Sunset glow fundus 2. Sugiura signiii. Other ocular signs 1. Nummular chorioretinal depigmented scars 2. RPE clumping 3. Recurrent or chronic anterior uveitis
4. Neurological/auditory findings (a) Meningismus (b) Tinnitus (c) Cerebrospinal fluid pleocytosis
5. Integumentary findings (a) Alopecia (b) Poliosis (c) Vitiligo

Complete VKH requires 1 to 5
Incomplete VKH requires 1 to 3 and either 4 or 5
Probable VKH requires criteria 1 to 3 only
Read et al. 2021 [18]

New criteria for early and late-stage VKH were also formulated using machine learning algorithms by the Standardization of Uveitis Nomenclature (SUN) Working Group, demonstrating low rates of misclassification (8.0% and 7.7% in the learning and validation sets for early-stage VKH and late-stage VKH 1.0% and 12%, respectively) and good performance as classification criteria for clinical research (overall accuracy for panuveitis was 96.3% in the training set and 94.0% in the validation set, and the machine learning equivalent to specificity was 94.4% for early-stage VKH) [12]. Unlike the Chinese criteria, the SUN criteria propose a short list of relevant specific diagnoses to exclude, reducing complexity and improving usability. Despite the advances, some criticisms regarding the specificity have been made. There are concerns that some other conditions associated with serous retinal detachment and septae on OCT can be classified as VKH using these criteria.

A recent Chinese study compared the performance of the RDC, DCV, and SUN criteria and found a higher sensitivity value and more extensive area under the curve (AUC) in DCV. The sensitivities, specificities, and AUCs were 92.2%, 96.1%, and 0.942 in DCV, 66.7%, 97.7%, and 0.822 in RDC, and 54.3%, 99.2%, and 0.767 in SUN criteria, respectively [13].

Treatment

The standard therapy includes high doses of systemic corticosteroids besides topical medications for anterior uveitis. Prednisone should be used orally in a typical dosage of 1 to 2 mg/kg/day. There is no evidence of the superiority of intravenous to oral corticosteroid use, but some authors recommend methylprednisolone in pulse therapy, particularly in more severe cases. Early steroid therapy followed by a slow taper in 6 to 9 months is advised. This approach has improved the prognosis by reducing the length of disease, the incidence of a convalescent phase, and decreasing extraocular manifestations in VKH. In refractory cases or in those where it is necessary to withdraw the steroid administration more quickly, it is essential to use systemic immunosuppressants, such as cyclosporine, cyclophosphamide, azathioprine, mycophenolate mofetil, and methotrexate. More recently, studies have also demonstrated the efficacy of immunobiological agents, such as adalimumab, infliximab, and rituximab, in treating VKH. For choroidal neovascular membranes, treatment options encompass traditional photocoagulation therapy or, more recently, intraocular antiangiogenic drug therapy. Acute angle closure glaucoma in the acute phase of the disease typically resolves after appropriate steroid treatment [14, 15].

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Orbital Myositis

95

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Abstract

Orbital myositis (OM) is a rare syndrome, but it represents the second cause of extraocular muscle compromise, after thyroid orbitopathy.

It is usually idiopathic and a diagnosis of exclusion, but it can also be associated with autoimmune or infectious diseases, paraneoplastic phenomena, or medications. Clinically, it is characterized by the triad of unilateral eye pain exacerbated by movement, diplopia, and conjunctival hyperemia. Imaging, with CT-scan or magnetic resonance, is useful for the diagnosis. An early diagnosis allows a good response to corticosteroids that represent the treatment of choice.

Keywords

Orbital · Myositis · Extraocular muscles · Imaging · Corticosteroids

Orbital myositis (OM) is an autoimmune disorder that mainly affects extraocular muscles, usually with unilateral involvement. Its early recognition allows effective treatment based on corticosteroid therapy with an acceptable response, while chronic cases degenerate into fibrosis with residual strabismus.

Epidemiology

Although there is no clear predominance, some studies show a mild predominance in women, with a ratio of 1.4:1 [1]. Described in different stages of life, the mean age is usually around 36 years [2].

Clinical Manifestations

OM is characterized by acute symptoms with a characteristic triad:

1. Orbital pain, exacerbated with the ocular movement.
2. Diplopia (due to paresis of the affected eye).
3. Conjunctival or palpebral edema or erythema (especially in the area of insertion of the affected muscle).

Only one muscle is affected in most cases, usually the medial rectus muscle, following by the lateral rectus, superior rectus, inferior rectus, obliques, and elevator muscles. It is more frequently presented as recurrent or metachronous/synchronous involvement [3]. A “migratory” OM has been described, meaning the involvement of several muscles in a recurrent presentation [2].

Diplopia is due to the muscle edema (initial stage) or fibrosis secondary to chronic inflammation. When there is fibrosis, recovery is usually not completely possible.

OM can be classified as idiopathic or secondary to several disorders (Tables 95.1 and 95.2).

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Table 95.1 Orbital myositis classification

Idiopathic	
	Acute single muscle
	Acute multimuscular
	Subacute
	Recurrent
	Chronic
Associated with local or systemic conditions	
	Infectious: Bacterial, viral or parasitic
	Autoimmune diseases
	Systemic inflammatory diseases
Secondary to medications	
Paraneoplastic	

Table 95.2 Entities associated with orbital myositis

Autoimmune diseases	
	IgG4-related disease
	Inflammatory bowel disease
	Sarcoidosis
	ANCA-associated vasculitis
Myositis caused by drug reactions	
	Ipilimumab and other checkpoint inhibitor
	Alemtuzumab
	Bisphosphonates
	Statin
	Interferon a-2b
	Ribavirin
Paraneoplastic	
	Breast carcinoma
	Seminoma
	Lung carcinoma
	Lymphoma
	Paraganglioma

Biochemical Features

Blood tests are usually within the normal values. Mild elevations of C reactive protein (CPR) and erythrocyte sedimentation rate (ESR) can be present. Eosinophilia has been occasionally described. Antinuclear autoantibodies can be detected in a percentage of patients with an unspecific pattern and in low titers [4].

Imaging

Imaging techniques, such as computed tomography (CT) scan or magnetic resonance imaging (MRI), can detect thickening and enhancement of the affected muscle belly, with occasional involvement of the muscle tendon (Fig. 95.1). Muscle involvement is fusiform and has well-defined limits, unlike what happens if there is an associated systemic disease [2, 4].

Malignancy needs to be ruled out if focal, nodular, or heterogeneous muscle involvement is detected. On the other hand, involvement of nonmuscular structures helps us to suspect other pathologies such as (Table 95.2):

1. Lacrimal gland involvement: sarcoidosis, lymphoma, IgG4-related disease.
2. Infraorbital nerve infiltration: IgG4-related disease, reactive lymphoid hyperplasia.
3. Orbital fat or optic nerve leaf: lymphoma, breast cancer metastasis.
4. Systemic symptoms: malignancies, infectious, autoimmune (granulomatosis with polyangiitis).

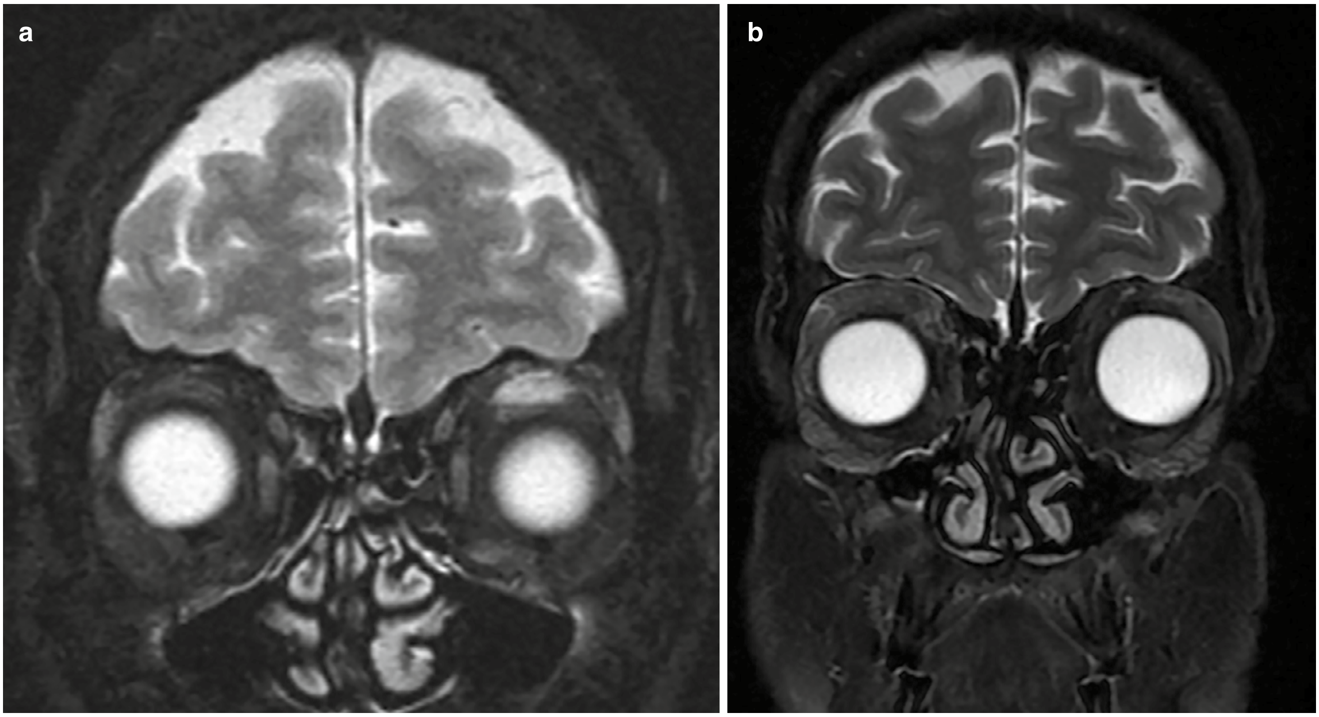

Fig. 95.1 MRI showing contrast enhancement in the upper eyelid and the superior rectus of the left eye (**a**). MRI showing involvement of the superior rectus muscle and the levator palpebrae superioris of the right eye (**b**)

Pathological Features

Histological study is not always necessary in OM because diagnosis is usually performed based on clinical and imaging findings. A biopsy is mandatory in inconclusive or atypical cases: patients with no pain, latent symptoms, involvement of all extraocular muscles, nodular/focal involvement, or involvement of adjacent nonmuscular structures.

Typical histological findings of OM are a polymorphous infiltrate with well-differentiated lymphocytes, plasma cells, neutrophils, and eosinophils. There are occasionally histiocytes and macrophages. The presence of granulomatous inflammation, vasculitis, and necrosis excludes the diagnosis of OM [2, 4].

Diagnosis

There are no definitive criteria for the diagnosis of OM. In 2008, Prieto and Grau proposed the following diagnostic criteria for OM. The diagnosis may be admitted when at least three of the four proposed criteria are present (Table 95.3) [2, 4–6]:

Clinical Criteria

- Eye pain: fundamental and characteristic element, exacerbated by the movement towards the affected muscle.
- Temporality: typically, acute (over days) or, in some cases, subacute.
- Unilateral: muscle involvement is mostly unilateral; patients with bilateral involvement, either synchronously or simultaneously, should raise the suspicion of an underlying systemic autoimmune disorder.
- Age: extremes of life are not usually affected.
- No association with systemic entities, except inflammatory bowel disease.
- Symptoms such as eyelid edema, eyelid ptosis, proptosis, diplopia, xerophthalmia, and decreased visual acuity are considered nonspecific symptoms.

Table 95.3 Diagnostic criteria for orbital myositis[a]

1. Unilateral orbital pain (+/− ophthalmoparesis)
2. Positive image test of muscle involvement without bone compromise
3. Satisfactory response to corticosteroid therapy
4. Compatible pathological examination

[a] Fulfilling the first three criteria, a probable case is admitted, and with the fourth item, a definite form

Imaging Criteria

CT and MRI are equally valid options for the evaluation of OM. Muscle involvement and enlargement of the horizontal rectus muscle are the most characteristic involvement. Anterior tendon involvement constitutes another very indicative sign of OM.

Response to Corticosteroids

Defined as the improvement of the signs and symptoms within 48 hours following the administration of systemic glucocorticoids at high doses (usually1 mg/kg/day). However, some false positives have been described in lymphoma, sarcoidosis, IgG4-related disease, and vasculitis.

Compatible Pathological Examination

As mentioned, polymorphous infiltrate with well-differentiated lymphocytes, plasma cells, neutrophils, and eosinophils are the typical findings.

Differential Diagnosis

Graves' orbitopathy is the main diagnosis to rule out, so it is essential to perform a complete medical history and blood test to check thyroid function and autoantibodies. The main muscles affected by this disease are the inferior rectus, medial rectus, superior rectus, lateral rectus, and obliques.

OM has an atypical and recurrent presentation when associated with autoimmune pathologies and specific inflammatory entities. OM has been described as a condition event preceding giant cell myocarditis or inflammatory bowel disease.

Orbital myositis may be associated with other autoimmune/autoinflammatory processes and non-inflammatory pathologies such as neoplasms (lymphoma, metastases), storage diseases (amyloidosis), and vascular pathologies (Table 95.2) [3].

Treatment

Treatment depends on the severity and progression of the disease. Mild cases (mono-muscular involvement, mild pain, and/or no motility impairment) can be treated with high doses of nonsteroidal anti-inflammatory drugs. For moderate-severe cases (impaired motility), corticoids are the treatment of choice, preferably prednisone at the dose of 1 mg/kg/day. Patients with typical OM usually show significant improvement after 48 h, so the response to corticosteroids is considered a diagnostic test [2, 4, 7].

Published data show a high relapse rate, around 23 to 56%. Factors associated with recurrence are male sex, several muscle and bilateral involvement, lack of tendinous involvement, and poor initial response to corticosteroids [8, 9].

In corticosteroid-dependent cases, immunosuppressants or biological drugs constitute the second and third line of treatment, respectively. Methotrexate is a good option as a steroid-sparing agent, with an acceptable response. Infliximab has shown to be a good option for severe/recurrent cases [10–12].

In chronic cases (usually associated with a poor response to corticosteroids), a biopsy must be performed to confirm/exclude the diagnosis.

Diplopia can be treated acutely with monocular occlusion, and botulinum toxin is reserved for selected patients. In the case of established strabismus, surgery may be considered as therapy if there is no inflammatory activity [13].

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Part XII

Renal Autoimmune Diseases

IgA Nephropathy

96

Jordi Ara

Abstract

Primary IgA nephropathy (IgAN) is the most common cause of glomerulonephritis worldwide. The diagnostic hallmark is mesangial IgA staining on kidney biopsy. Patients may present with different clinical pictures, ranging from the classic form of macroscopic hematuria with proteinuria starting after upper respiratory tract infection, microhematuria with varying degrees of proteinuria with or without hypertension and with or without chronic kidney disease, and less frequently nephrotic syndrome, acute kidney injury (AKI), or rapidly progressive glomerulonephritis. The clinical course is highly variable. Approximately 15% of patients progress to end-stage chronic kidney disease within 15 years and 40% within 20 years of follow-up. Patients with persistent proteinuria of more than 1 g per day, impaired renal function at diagnosis, and high MEST score are considered to be at high risk for disease progression.

Treatment of IgA nephropathy aims to reduce progression and prevent chronic kidney disease. The KDIGO 2021 guidelines recommend supportive treatment including ACEI/ARB to maintain proteinuria below 1 g per day and blood pressure < o = 120/70. If proteinuria of more than 1 g persists after 3 months of optimized supportive treatment, glucocorticoids may be considered in patients with eGRF greater than 30 mL/min.

Keywords

IgA nephropathy · Epidemiology · Clinical course · Oxford classification · KDIGO · Treatment algorithm

Introduction

IgA nephropathy (IgAN) was first described in 1968 by Berger and Hinglais [1] and is now recognized as one of the most common forms of glomerulonephritis worldwide. IgAN is characterized on renal biopsy by dominant IgA glomerular deposits, usually accompanied by local cellular proliferation and matrix expansion. Recurrent visible hematuria concurrent with a febrile illness is the hallmark clinical feature of IgAN and is particularly common in children and young adults, whereas microscopic hematuria with or without varying degrees of proteinuria is frequently observed among adults. The clinical course of IgAN is highly variable, ranging from asymptomatic nonprogressive disease to very aggressive disease. Cohort analysis found a frequency of chronic kidney disease of 15% over 10 years and 40% over 20 years of follow-up. Currently, the diagnosis of IgA nephropathy requires a renal biopsy, as no sufficiently specific and sensitive biomarker is available to replace this procedure [2, 3].

Epidemiology [2–5]

IgAN can affect people of all ages but usually affects young adults (second to third decade of life) with a male predominance of 2–3:1. This entity occurs with greatest frequency in Asians and Caucasians and is relatively rare in blacks. The incidence of IgAN is reported to range from 0.25 to 5 per 100.000 individuals per year, with lower prevalence in North America and Europe (Spain 0.6 per 100.000 individuals per year) and higher prevalence in East Asian countries. Japan has the highest frequency with approximately 14 per 100.000 individuals per year, probably due to widespread screening of school-aged children for urinary abnormalities and genetic factors. Latent mesangial IgA deposition is detected in 1.3–6.8% of forensic necropsies and in 16% of renal allograft donors in Japan. The differences in incidence and prevalence observed between the different territories may be explained

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by genetic differences between different populations but also by the different criteria used to perform renal biopsies or screening programmes for urinary abnormalities.

Clinical Manifestations [2, 3, 6–8]

The clinical presentation of IgAN is highly variable and depends on the population studied. The most common clinical pictures of IgAN are as follows:

Asymptomatic Hematuria and Proteinuria

Asymptomatic urinary testing identifies 30–40% of patients with IgAN and is the most common presentation. These patients are usually adults with asymptomatic hematuria with varying degrees of proteinuria with or without hypertension or progressive renal disease. Asymptomatic hematuria with minimal proteinuria (<0.5 g/day) is considered to have a favorable prognosis. Patients with proteinuria greater than 1 g and hypertension usually progress to chronic kidney disease and persistent microhematuria is a poor prognostic factor. Actuarial renal survival at 10 years is reported to be 57–80%.

Synpharyngitic Macroscopic Hematuria

Approximately 10–15% of patients present with one or recurrent episodes of visible hematuria (described as "cola-colored"), usually following an upper respiratory tract infection. In contrast to 10- to 14-day delay in onset in patients with post-streptococcal glomerulonephritis, the urine turns red 1–2 days after the first infectious symptoms. Some patients also describe low back pain, often reflecting stretching of the renal capsule, low-grade fever, malaise, and myalgia. Hypertension and peripheral edema are rare. Gross hematuria resolves spontaneously within days, and episodes may recur months or years later with febrile illness or extreme exercise.

This presentation usually occurs in patients younger than 40 years and is associated with a favorable prognosis.

Nephrotic Syndrome

Nephrotic syndrome with normal urinary sediment and normal renal function is rare and represents only 5% of all patients with IgAN. The prognosis and response to prednisone treatment are very good.

Acute Kidney Injury (AKI)

(a) The decline in renal function in IgA nephropathy is usually chronically progressive, but on rare occasions, patients may develop AKI. Possible causes of AKI in IgAN are as follows: Abundant glomerular hematuria leading to acute tubular injury due to clogged red cell casts and/or heme toxicity. In patients with AKI after gross hematuria, improvement of renal function usually occurs within 1 to 2 weeks after disappearance of gross hematuria.
(b) AKI and hematuria due to concurrent anticoagulant related nephropathy can be the initial presentation of IgAN if patients are taking anticoagulants, especially dabigatran.
(c) Rapidly progressive glomerulonephritis.

Rapidly Progressive Glomerulonephritis (RPGN)

IgAN with rapidly progressive course is rare and is frequently associated with a pathologic finding of >50% of glomeruli exhibiting crescents (RPGN). This syndrome may appear at presentation or during the course of IgAN and may occur in the absence of any clinical features of IgA vasculitis. The prognosis is very poor, with a 1-year end-stage renal disease rate of 42% despite immunosuppressants.

Crescents are frequently seen in patients with IgAN and need not be accompanied by RPGN. The presence of rare crescents does not mandate the use of immunosuppressive therapy, but crescents in IgAN identify patients with a poor renal outcome.

Malignant Hypertension

Rarely, IgAN may present with malignant hypertension.

Chronic Kidney Disease

Some patients present renal failure, proteinuria, and hypertension when first diagnosed. The smaller size of the kidneys makes renal biopsy difficult. These patients are usually older and are likely to have long-standing disease that was not detected earlier because the patient did not have hematuria or did not undergo routine testing.

Other Diseases with IgA Deposition

Schönlein-Henoch Purpura

Schönlein-Henoch purpura is an IgA-mediated small-vessel vasculitis affecting the skin, joints, gut, and kidney in which the glomerular disease is indistinguishable from IgAN . Apart from the typical systemic signs of vasculitis, the clinical differences between the two entities are as follows: a) Peak age is lower in Schönlein-Henoch purpura (<15 years) than in IgAN (> 15 years). b) Acute hematuria and/or massive proteinuria are much more frequent in Schönlein-Henoch purpura than in IgAN (>15 years). c) Schönlein-Henoch purpura is more frequently described in association with drug hypersensitivity. d) Schönlein-Henoch purpura is much less frequently associated with other diseases than IgAN.

Secondary Forms of IgA Nephropathy

In the vast majority of cases, IgAN is an isolated disease (primary IgAN), but it may be associated with various clinical disorders. The causes of secondary IgAN are summarized in Table 96.1.

Pregnancy and IgAN [9]

Pregnancy in women with IgAN can pose challenges due to the potential impact on maternal and fetal health. The effect of pregnancy on the course of IgAN is not well-established nor are the maternal-fetal risks of pregnancy in women with this disease. Most women with IgAN will have a favorable pregnancy outcome, although they are at increased risk of preterm birth, pregnancy induced hypertension, preeclampsia, and cesarean section. Absolute risks of intrauterine or neonatal death were low. Finally, pregnancy in IgAN was not associated with increased progression of renal disease.

Table 96.1 Diseases reported in association with IgA nephropathy

Diseases reported in association with IgA nephropathy
• Schönlein-Henoch purpura
• Hepatic disease (non-alcoholic cirrhosis, alcoholic, liver disease)
• Intestinal disease (Crohn's disease ulcerative colitis, celiac disease)
• HIV infection
• Glomerulonephritis (lupus nephropathy, minimal change disease, membranous nephropathy)
• Skin diseases (psoriasis, dermatitis herpetiformis)
• Systemic/immunological disorders (systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, Reiter's syndrome, uveitis, Bechet's syndrome, Takayasu's syndrome, myasthenia gravis, sicca syndrome)
• Malignancy (small cell carcinoma, lymphoma, Hodgkin's disease, T-cell lymphomas including mycosis fungoides, IgA monoclonal gammapathy)
• Respiratory disease (tuberculosis, bronchiolitis obliterans, sarcoidosis)
• Infections (B hepatitis, brucellosis, leprosy)

Pathology [2, 3, 10, 11]

A renal biopsy demonstrating dominant or codominant mesangial IgA staining is required for definitive diagnosis.

Light Microscopy

The features of IgAN on light microscopy can vary greatly between patients and within the same individual sample and may reveal mesangial matrix expansion, mesangial or endocapillary hypercellularity, and sometimes crescents. Global or segmental glomerulosclerosis, tubular atrophy, and interstitial fibrosis are usually seen in patients with advanced disease (high proteinuria or chronic kidney disease).

Immunofluorescence Findings

Histologically, IgAN (as the name suggests) is characterized by the presence of diffuse mesangial IgA deposits that are visible by immunofluorescence techniques. At the same time, deposits of C3 (90% of cases), IgG (40% of cases), and IgM (40% of cases) may also be observed, but no deposits of c1q are found. Occasionally, IgA deposits may also be seen in the capillary wall, though this is much more typical in Schönlein-Henoch purpura nephropathy than in primary IgAN. When present in IgAN, it is associated with a worse prognosis.

Electron Microscopy

Electron microscopy should confirm immunofluorescence findings with immune electron-dense deposits in the mesangium with or without subendothelial deposits.

Oxford Classification [10, 11] (Table 96.2)

The Oxford classification of IgAN was first published in 2009 by a working group of nephrologists and renal pathologists representing the International IgA Nephropathy Network and the Renal Pathology Society. In this study, with a cohort of 265 patients with >0.5 g/day of proteinuria, eGFR > o = 30 mL/min, >o = 1 year of follow-up, and renal biopsy

Table 96.2 MEST Score

Pathologic feature	Definition	Scoring system
Mesangial hypercellularity (M)	≥4 mesangial cells in any mesangial area of a glomerulus	M0: Mesangial hypercellularity in ≤50% of glomeruli M1: Mesangial hypercellularity in >50% of glomeruli
Endocapillary hypercellularity (E)	An increased number of cells in glomerular capillary lumen	E0: Absence E1: Presence of any glomeruli showing endocapillary hypercellularity
Segmental glomerulosclerosis (S)	Adhesion or sclerosis that not involving the entire glomerulus	S0: Absence S1: Presence of any segmental glomerulosclerosis (podocyte hypertrophy/tip lesions should be noted if present)
Tubular atrophy/interstitial fibrosis (T)	The percentage of tubular atrophy/ interstitial fibrosis of cortical area	T0: 0–25% T1: 26%–50% T2: >50%
Cellular/fibrocellular crescents (C)	Extracapillary cell proliferation >2 cell layers thick and <50% matrix	C0: Absence C1: Presence of cellular/fibrocellular crescents in <25% of glomeruli C3: Presence of cellular/fibrocellular crescents in ≥25% of glomeruli

At least 8 viable glomeruli are required for MEST-C score

with a minimum 8 glomeruli, four key pathologic features (MEST) were consistently and independently associated with poor renal outcome: mesangial hypercellularity (M), endocapillary cellularity (E), segmental glomerulosclerosis (S), and tubular atrophy and segmental glomerulosclerosis (T). The absence/presence of >50% of glomeruli showing mesangial hypercellularity is denoted M0/M1, respectively. E1 indicates endocapillary hypercellularity, S1 denotes any segmental glomerulosclerosis, and T0,T1 and T2 reflect fibrosis affecting 1–25%, 26–50%, or > 50%, respectively, of the cortical area. In a larger study, crescents also predict outcome (C0, no cellular or fibrocellular crescents; C1, crescents <25%; and C2, crescents >25% glomeruli) and now recommend C to be added to the MEST score.

Since 2009, this classification has been widely used in clinical practice, and the clinical relevance and applicability of this score has been validated across multiple studies and populations.

Diagnosis [2, 3]

The diagnosis of IgAN is always made by renal biopsy demonstrating the presence of this immunoglobulin in the glomerular mesangium by immunofluorescence techniques. Although a compatible clinical picture (synpharyngitic macroscopic hematuria) would be highly suggestive, it is insufficient for the diagnosis, and moreover, in the great majority of cases, the clinical and laboratory data do not indicate whether it's IgAN or another type of glomerulonephritis. Analytically, approximately one-third of patients with IgAN have elevated serum IgA levels, but this is of no diagnostic value. At present, there are no diagnostic criteria combining clinical, biochemical, and immunological data that are useful for this disease. Consequently, performing a renal biopsy remains essential for the diagnosis and prognosis of IgA nephropathy.

The main problem is deciding the most appropriate time to conduct the biopsy. An aggressive approach to biopsy criteria (microhematuria alone or microhematuria with minimal proteinuria) would increase the number of cases diagnosed but would have little relevance in changes in therapeutic attitudes, in addition to increasing the number of patients undergoing renal biopsy and the inherent risks.

Although there is no global agreement on the indication, it seems reasonable to consider a renal biopsy in patients with suggestive clinical signs and:

(a) Microhematuria with proteinuria >1 g daily.
(b) Microhematuria with proteinuria and renal failure.

Since the forms of the disease with good prognostic criteria (isolated hematuria or hematuria with minimal proteinuria) have a certain risk of progression, clinical monitoring of these non-biopsied patients is recommended, as well as a change of attitude if the above criteria are met.

New Biomarkers [4, 12]

In recent years, significant progress has been made in identifying potential biomarkers that may be useful in the future. These biomarkers are often related to the pathogenesis of IgAN, such as serum levels of galactose-deficient IgA (Gd-IgA1) 1 or antibodies (IgA or IgG) to galactose deficient IgA1 produced due to exposure to N-acetylgalactosamine residues. These residues act as a neoepitopes and stimulate the synthesis of these antibodies. The pathogenesis of IgAN is summarized in Fig. 96.1. Moldoveanu et al. first investigated the quantification of serum Gd-IgA1 levels as a diag-

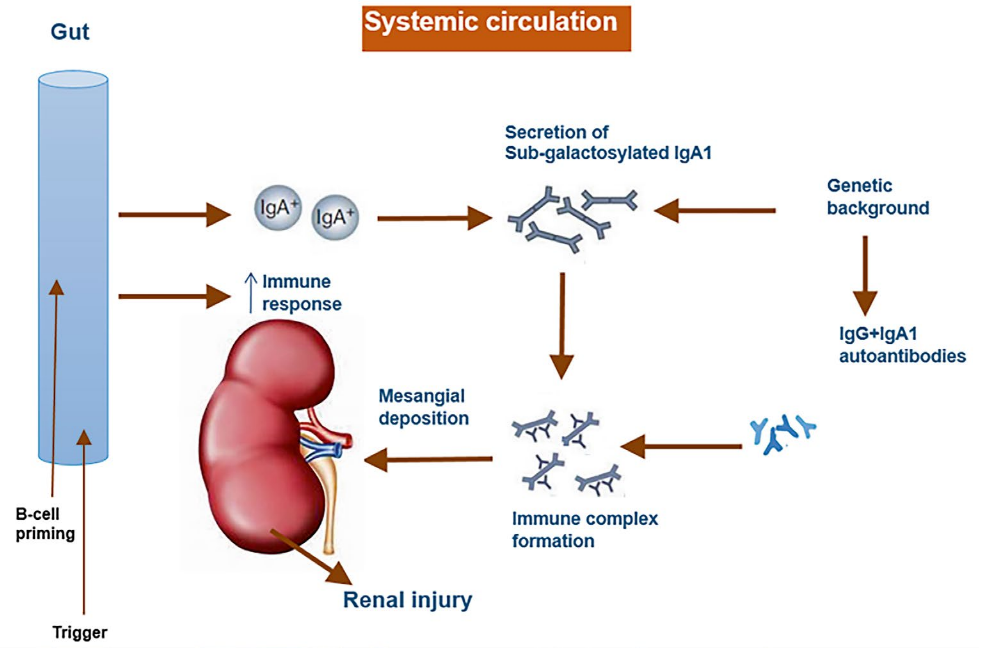

Fig. 96.1 Pathogenesis of IgAN

nostic test (sensitivity 77%/specificity 90%). Elevated serum levels of IgA, Gd-IgA1, Gd-IgA1-specific IgG, and Gd-IgA1-specific IgA were observed in patients with IgAN compared with those of healthy controls and patients with other renal diseases . Gd-IgA1-specific IgG showed the best performance for the diagnosis of IgAN, with a sensitivity of 89% and a specificity of 92%. Although these biomarkers may be useful for the diagnosis of IgAN, there is substantial overlap in serum levels of individual biomarkers between patients with IgAN, other renal diseases, and healthy controls. Despite their high sensitivity, neither subgalactoside IgA levels nor anti-IgA antibodies are available in daily clinical practice.

Clinical Course and Progression Factors [2, 3, 14]

The evolution of IgAN is highly variable and ranges from very benign to rapidly progressive renal impairment. In general, this entity is considered a disease that progresses slowly to renal failure, as evidenced by the fact that approximately 15% of diagnosed patients will enter hemodialysis programmes at 10 years and 40% at 20 years of follow-up. A retrospective study of a large series of patients with this disease enabled us to establish the factors that considered to be key in the progression of the disease. The factors indisputably linked to a poor prognosis from the clinical point of view are elevated creatinine at the time of diagnosis, hypertension, and proteinuria >1 g daily.

Several studies suggest that the risk of progression to chronic kidney disease is proportional to the proteinuria at 1-year follow-up: patients with proteinuria <0.5 0.5 g/day have a 0% risk of progression at 5-year follow-up, patients with proteinuria between 0.5 and 1.5 g/day have a 13% risk, those with proteinuria between 1.5 and 3 g/day have a 25% risk, and finally, patients with proteinuria >3 g have a 60% risk of progression to chronic kidney disease. Given the close relationship between incremental changes in proteinuria and disease risk, we recommend using 24-h urine collections to discern smaller gradations of proteinuria. In patients with biopsy-proven glomerulonephritis, the urine protein-creatinine ratio (UPCR) correlates relatively poorly with 24-h urine protein excretion, particularly when proteinuria is greater than 1 g/day.

Obesity and smoking are also likely to contribute directly and indirectly to renal risk.

Recently, an international IgA prediction tool has been developed to predict the risk of a 50% decrease in eGFR or renal failure by incorporating clinical (age, blood pressure, eGFR, ACEI ARB use) and histological parameters (MEST) at the time of biopsy. The prediction tool is available online (https://qxmd.com/calculate) [13].

Treatment [14–17]

The proposed treatment scheme based on the KDIGO guidelines is summarized in Fig. 96.2. The KDIGO Guidelines for the management of glomerular disease, the

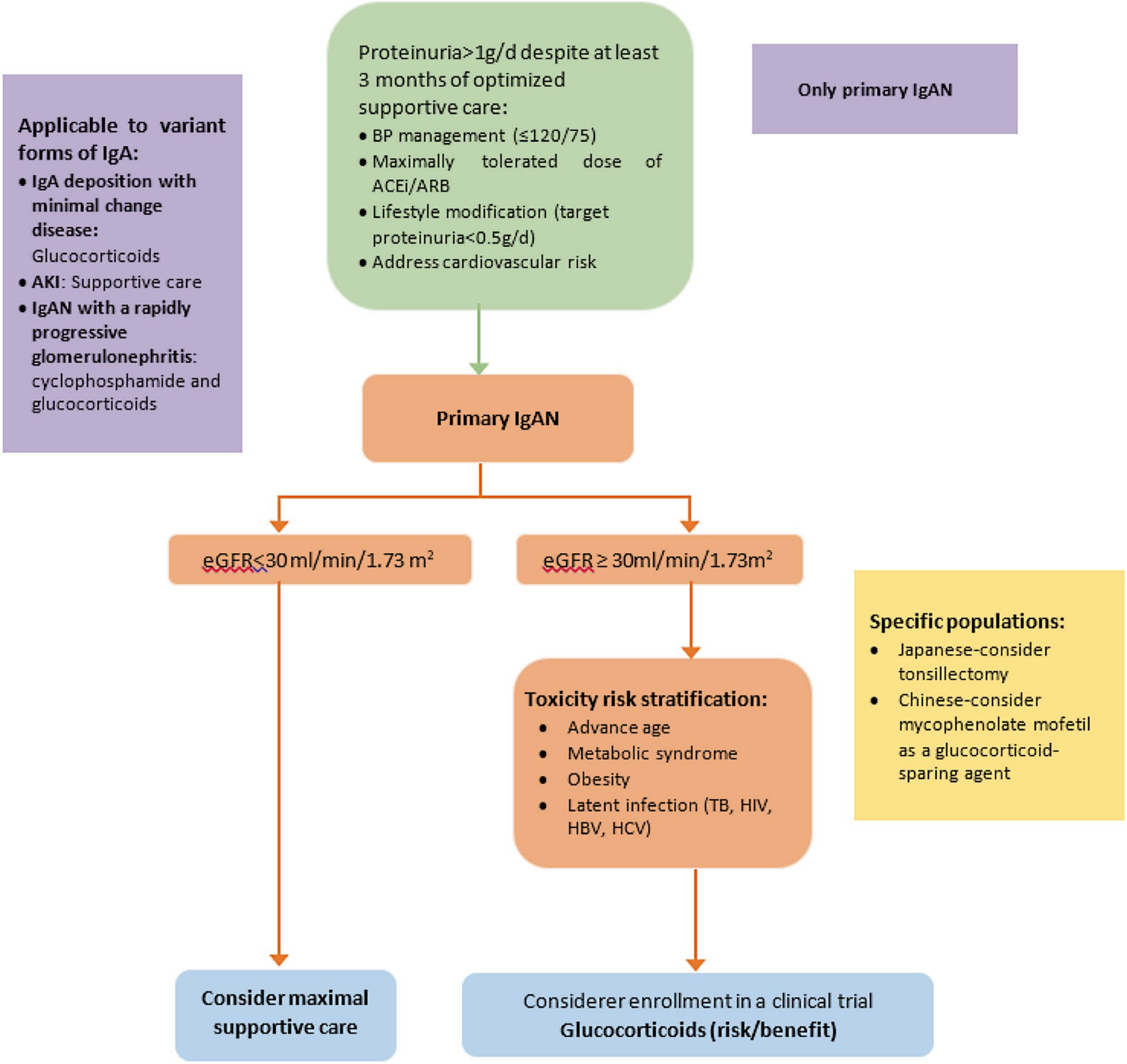
Applicable to variant forms of IgA:
• IgA deposition with minimal change disease: Glucocorticoids
• AKI: Supportive care
• IgAN with a rapidly progressive glomerulonephritis: cyclophosphamide and glucocorticoids
Proteinuria>1g/d despite at least 3 months of optimized supportive care:
• BP management (≤120/75)
• Maximally tolerated dose of ACEi/ARB
• Lifestyle modification (target proteinuria<0.5g/d)
• Address cardiovascular risk
Only primary IgAN
Primary IgAN
eGFR<30 ml/min/1.73 m²
eGFR ≥ 30ml/min/1.73m²
Toxicity risk stratification:
• Advance age
• Metabolic syndrome
• Obesity
• Latent infection (TB, HIV, HBV, HCV)
Specific populations:
• Japanese-consider tonsillectomy
• Chinese-consider mycophenolate mofetil as a glucocorticoid-sparing agent
Consider maximal supportive care
Considerer enrollment in a clinical trial
Glucocorticoids (risk/benefit)

Fig. 96.2 Management of patients with IgAN. (Adapted from KDIGO guidelines)

primary goal of IgAN management (2021), recommends optimizing conservative treatment, including blood pressure control and HTA treatment, RAS blockade as much as tolerated (blood pressure target <125/75), cardiovascular risk minimization (treatment of dyslipidemia, low salt diet), and adherence to lifestyle advice, including dietary counseling, smoking cessation, weight control, and exercise. RAS blockade should be instituted independently of hypertension if the patient presents with proteinuria >0.5 g/d (Grade 1B).

If proteinuria remains above 0.75–1 g/d despite at least 90 days of optimized supportive care, the patient is at high risk for progressive loss of renal function, and glucocorticoid therapy for 6 months (Grade 2B) may be considered. In patients with eGFR <50–30 mL/min per 1.73 m^2, diabetes, obesity (body mass index >30 kg/m^2), or other situations, such as latent infections, liver cirrhosis, active peptic ulcer, uncontrolled psychiatric disease, or severe osteoporosis, glucocorticoid therapy should be clinically assessed for risks and benefits and also taking into account signs of renal biopsy activity and chronicity. Reduction of proteinuria to less than 1 g/d is a surrogate marker of improved renal outcome in IgAN and therefore a reasonable treatment goal for these patients.

Clinical forms of nephrotic syndrome with IgA deposition, similar to minimal change disease, show a good response to corticosteroid treatment.

Rapidly progressive IgA glomerulonephritis should be treated similarly to ANCA vasculitis.

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Membranous Nephropathy

97

Marc Xipell and Luis F. Quintana

Abstract

Membranous nephropathy (MN) is an autoimmune podocytopathy caused by the formation of immune complexes on the subepithelial surface of podocytes, leading to progressive thickening of the glomerular basement membrane. Clinically, it manifests as a nephrotic syndrome. Approximately, 80% of cases are a primary autoimmune disease limited to the kidney, also known as primary membranous nephropathy (pMN). In pMN, antibodies against the phospholipase A2 receptor (aPLA$_2$R) are identified in the vast majority of patients. In the remaining, MN is a secondary process, where the target antigen is associated with infections, drugs, neoplasms, or systemic diseases. The clinical course is variable, with spontaneous complete remission occurring in up to 30% of patients. Immunosuppressive therapy should be restricted to patients considered at risk for progressive kidney injury. The most commonly used treatments are rituximab and calcineurin inhibitors (CNIs) (especially tacrolimus) or a combination of them and the cyclic regimen of prednisone and cyclophosphamide (modified Ponticelli regimen). With current immunosuppressive treatments, the risk of end-stage renal disease has decreased to 10%.

Keywords

Nephrotic syndrome · Risk of progression · Chronic kidney disease · Autoimmune podocytopathy · Phospholipase A2 receptor (aPLA$_2$R)

Description of the Disease

Membranous nephropathy is an autoimmune podocytopathy caused by the formation of immune complexes on the subepithelial surface of podocytes, leading to the fusion of podocyte processes and progressive thickening of the glomerular basement membrane (GBM). Consequently, large amounts of protein are lost through the urine, which manifests clinically as a nephrotic syndrome [1]. These immune complexes are constituted by antibodies directed against podocyte antigens and by components of the complement system. It is the most common cause of nephrotic syndrome in nondiabetic adults and may recur in the kidney allograft. Its incidence is 5–10 cases/million inhabitants, and it usually manifests in the fifth and sixth decade of life, with a predominance in men (2:1) [2].

At least 80% of cases are a primary autoimmune disease limited to the kidney, also known as primary membranous nephropathy (pMN). In pMN, antibodies against the phospholipase A2 receptor (aPLA$_2$R) are identified in 75% of patients [3], and antibodies against the thrombospondin 7A type 1 protein (THSD7A) are found in 5% of patients [4]. In both cases, the predominant subclass is IgG4. Other antigens have been described in very short series of patients with pMN, such as NELL-1, Sema3B, EXT1, EXT2, NCAM1, PCDH7, and HTRA1 [5].

In the remaining 20%, membranous nephropathy is a secondary process, where the target antigen is associated with infections, drugs, neoplasms, or systemic diseases (Table 97.1).

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Table 97.1 Diseases associated with membranous nephropathy

Infections	HBV, HCV, HIV, malaria, schistosomiasis, syphilis, endocarditis, hydatidosis, filariasis, leprosy
Neoplasms	Lung, gastrointestinal, breast, lymphoma, kidney, ovary, leukemia, mesothelioma, prostate
Drugs/toxics	NSAIDs, gold, penicillamine, captopril, clopidogrel, lithium, hydrocarbons, mercury, COX-2 inhibitors
Autoimmune diseases	Systemic lupus erythematosus, thyroiditis, rheumatoid arthritis, mixed connective tissue disease, ankylosing spondylitis, dermatomyositis, scleroderma, myasthenia gravis, Sjögren's syndrome, Crohn's disease, temporal arteritis, graft-versus-host-disease

However, this distinction between primary or secondary MN is increasingly controversial, and the use of an antigen- and associated disease-based classification (if any) is preferred [6].

Signs and Symptoms

Characteristically, patients with MN present proteinuria, 80% in the nephrotic range and 30% accompanied by microhematuria. Clinically, it presents as a nephrotic syndrome. Patients may present infectious complications or thrombosis secondary to nephrotic syndrome. Hypertension at presentation is uncommon (<20% of patients). In the early stages, it is not associated with deterioration of renal function, except in cases in which there are complications, such as renal vein thrombosis, diuretic overdose, or, very rarely, extracapillary proliferation. However, disease progression with sustained proteinuria over time can lead to end-stage chronic kidney disease.

The clinical course is variable, with spontaneous complete remission (CR) occurring in up to 30% of patients in the absence of immunosuppressive treatment. Twenty-five percent of patients with CR can present relapses, so follow-up is recommended. Renal survival at 10 years is 100% in patients with CR, 90% in those with partial remission (PR), and 50% if remission is not achieved. With current immunosuppressive treatments, the risk of end-stage renal disease has decreased to 10%. Poor prognostic factors are age >50 years, male sex, persistent proteinuria >8 g, arterial hypertension, GFR <30 mL/min/m^2, and histological data of global glomerulosclerosis, tubulointerstitial fibrosis, and vascular damage.

Laboratory Findings

Laboratory tests should include complete blood count, CRP, coagulation, ionogram, liver and kidney function, serum albumin, serum proteins, and erythrocyte sedimentation rate, but these results are not specific. Main laboratory findings are summarized in Table 97.2.

Table 97.2 Laboratory findings

Proteinuria	100%
Nephrotic range proteinuria	80%
Microscopic hematuria	30%
Hypoalbuminemia	>90%
Hyperlipidemia (↑ cholesterol, VLDL/LDL, triglyceride)	>90%

Approximately 75% of patients with pMN have autoantibodies against PLA$_2$R (aPLA$_2$R), which are highly specific for the disease. The most used technique for its detection is by enzyme-linked immunosorbent assay (ELISA), which has a sensitivity of 68% and specificity of 97% [7]. A result of aPLA$_2$R $\geq$20 RU/mL is considered positive, and aPLA$_2$R < 14 RU/mL is considered negative. The range between 14 and 19 RU/mL is considered uncertain. In patients with negative aPLA$_2$R, the determination of antibodies against other antigens is indicated, especially anti-THSD7A, and it is essential to rule out secondary causes.

Immunological tests, serum protein electrophoresis, and serological analysis (HIV, HCV, HBV...) can provide guidance on secondary causes of the disease. Other studies are recommended in patients with pMN of unknown antigen or if neoplasia is clinically suspected, such as chest x-ray, abdominal ultrasound, urinary cytology, PET/CT, and gastrointestinal endoscopy, among others.

Diagnostic Criteria

The diagnosis of MN is made by kidney biopsy, and it is always recommended to assess the stage of the disease. However, in selected patients with nephrotic syndrome and a positive aPLA$_2$R antibody test, the diagnosis of pMN can be made with high confidence without biopsy when there is a contraindication to biopsy.

Light Microscopy in the very early stages of the disease, the histology of the glomerulus is normal. Subsequently, perpendicular projections of the basement membrane (spikes) can be observed in silver staining. These can encompass the deposits, producing a diffuse thickening of the glomerular basement membrane, even with the loss of density of the deposits. In the long term, signs of chronic damage may be found, including glomerular sclerosis, interstitial fibrosis, and tubular atrophy. These features are associated with a worse kidney prognosis. Currently, immunohistochemical staining of fixed tissues of PLA$_2$R and THSD7A is mandatory.

Immunofluorescence Granular deposits of IgG+++ and C3+ on the subepithelial surface of the GBM. Immunofluorescence for PLA_2R and THSD7A, as well as IgG4, is also recommended.

Electron Microscopy Electron-dense deposits on the subepithelial surface of the GBM and expansion of the GBM due to deposition of new extracellular matrix between the deposits (spikes).

Histological signs suggesting secondary disease are as follows: deposits of immune complexes in the mesangium and subendothelium, along the tubular basement membrane and vessel walls; mesangial and endocapillary proliferation; C1q deposition; *full-house* deposition in immunofluorescence; tubuloreticular structures in endothelial cells in electron microscopy (especially SLE); absence of colocalization of PLA_2R and IgG4; and positivity for another immunoglobulin subclass other than IgG4 (IgG4 is the predominant subclass in pMN associated with PLA_2R and THSD7A) [8].

Risk Stratification

The risk of progression is marked by the degree of proteinuria, renal function, serum albumin, and $aPLA_2R$ levels [9, 10]. Its importance lies in prognosis, renal survival, and treatment of the disease. According to KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases [11], there are four risk groups (Table 97.3):

1. Low risk: proteinuria <3.5 g/24 h, albumin >3 g/dL, normal eGFR; OR, proteinuria <3.5 g/24 h, normal eGFR or a decrease of proteinuria >50% in 6 months of conservative treatment (ACE inhibitors/ARBs).
2. Moderate risk: normal eGFR, proteinuria between 3.5 and 8 g/24 h and without a reduction of at least 50% after 6 months of supportive treatment and without meeting high/very high-risk criteria.
3. High risk:
   (a) GFR <60 mL/min/1.73 m^2 and/or proteinuria >8 g/24 h that persists for more than 3–6 months.
   (b) Normal eGFR, proteinuria >3.5 g/24 h, and no >50% decrease after 6 months of conservative treatment AND at least one of the following: albumin <2.5 g/dL, $aPLA_2R$ >50 UI/mL during the first 3 months of observation. Patients with anasarca or complicated edema will also be considered of high risk.
4. Very high risk: life-threatening nephrotic syndrome and/or rapid worsening of kidney function not explained by other causes.

Table 97.3 Stratification of the risk of progression of membranous nephropathy

	Proteinuria	eGFR	aPLA2R (trend of the first 3 months)	Albumin
Low	<3.5 g/d, or >50% reduction in 6 months	Normal	<50 UI/mL	>2.5 g/dL
Moderate	3.5–8 g/d and no reduction of >50% in 6 months	Normal	<50 UI/mL	>2.5 g/dL
High	>8 g/d that persists more than 3–6 months	<60 mL/min/1.73 m^2	>50 UI/mL	<2.5 g/dL
Very high	Severe nephrotic syndrome	Rapid worsening of kidney function	>150 UI/mL	<1.5–2 g/dL

Adapted from KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases

Therapy

All patients will receive optimal nephroprotective treatment from the diagnosis of the disease: adequate diet, physical activity, avoidance of smoking, normal weight, normal blood pressure, use of ACE inhibitors and ARBs to control proteinuria, control of dyslipidemia, etc. In case of severe hypoalbuminemia (<25 g/L), prophylactic anticoagulation with LMWH is recommended. In the event of thrombosis, anticoagulation will be used at therapeutic doses until the resolution of the nephrotic syndrome and for a minimum of 6 to 12 months, if there are no contraindications.

Immunosuppressive therapy should be restricted to patients considered at risk for progressive kidney injury. The most commonly used treatments are rituximab and calcineurin inhibitors (CNIs) (especially tacrolimus), or a combination of them, and the cyclic regimen of prednisone and cyclophosphamide (modified Ponticelli regimen) (Table 97.4). The regimen of choice will depend on the patient's profile, the risk of progression, and whether it is a first episode, a refractory disease, or a relapse. The cyclical regimen of prednisone and cyclophosphamide produces remission (complete or partial) in the vast majority of patients, although it is reserved for very high-risk patients due to its high risk of toxicity [12]. Rituximab as monotherapy induces remission of proteinuria and $aPLA_2R$ titer and is considered the first option for moderate and high-risk patients, although the evidence is still considered moderate [13, 14]. The use of tacrolimus as monotherapy also induces disease remission but is associated with a high relapse rate [15]. Therefore, in many cases, the combined use of both therapies (RTX + CNI) is considered to consolidate the response [16, 17].

In low-risk patients, expectant management is recommended for 3 to 6 months, given the probability of spontaneous remission. In patients at moderate risk, although watchful waiting may also be an option in some cases, early initiation of immunosuppressive treatment will be the common option. In these cases, the combination of rituximab with tacrolimus is the most established, although monotherapy treatment can also be performed. A treatment option would be to administer 1 g (×2) of rituximab initially, followed by full-dose tacrolimus for 6 to 9 months, with a subsequent taper over another 6 months. Another option would be to start tacrolimus first and administer 1 or 2 g of rituximab after 6–9 months, to consolidate the therapeutic response before gradually tapering tacrolimus. In patients with resistant disease, the use of regimens based on cyclophosphamide (whether or not associated with rituximab) will be initially considered [11].

All patients will undergo close follow-up, with serial monitoring of renal function, proteinuria, and $aPLA_2R$ titer. A high titer or increase in $aPLA_2R$ over time is associated with disease recurrence, which usually precedes increasing proteinuria. The evolution of antibody titer over time may be more useful in identifying patients who will experience recurrence/remission compared to a single baseline measurement [18]. During immunosuppressive treatment, close surveillance of opportunistic infections will be carried out. Finally, it is recommended to screen for latent infections, review the vaccination schedule, and preserve fertility.

Table 97.4 Treatment options and dosage schemes (adapted from KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases)

Cyclophosphamide	Option A (cyclical)
	Methylprednisolone 1 g iv for 3 consecutive days at the start of months 1, 3, and 5
	Prednisone 0.5 mg/kg/d in months 1, 3, and 5
	Oral cyclophosphamide 2–2.5 mg/kg/d in months 2, 4, and 6
	Option B (continuous)
	Methylprednisolone 1 g iv for 3 consecutive days at the start of months 1, 3, and 5
	Prednisone 0.5 mg/kg/d every other day in months 1–6, with taper thereafter
	Oral cyclophosphamide 2–2.5 mg/kg/d in months 1–6
	Option C (cyclical, with iv CYC)[a]
	Methylprednisolone 1 g iv for 3 consecutive days at the start of months 1, 3 and 5
	Prednisone 0.5 mg/kg/d in months 1, 3, and 5
	IV cyclophosphamide 10–15 mg/kg the first day of months 2, 4, and 6
Rituximab	Option A: Rituximab 1 g iv administered twice within 2 weeks
	Option B: Rituximab 375 mg/m^2 given 1–4 times at weekly intervals
Tacrolimus	Oral tacrolimus 0.05–0.1 mg/kg/d, target trough level 5–8, duration 12–15 months
Cyclosporine	Oral cyclosporine 3.5 mg/kg/d, target trough level 125–225 ng/mL

[a] There are no RCTs evaluating the efficacy of intravenous cyclophosphamide in MN. However, it might be considered in patients in whom a lowest possible cumulative dose should be used

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Minimal Change Disease

98

Marc Xipell and Luis F. Quintana

Abstract

Minimal change disease (MCD) is a podocytopathy that is the main cause of nephrotic syndrome in childhood (up to 90% of cases), being less frequent in adults (10–15%). The pathogenesis of the disease includes the interaction of several factors, such as genetics—mutations that cause structural or functional abnormalities in podocytes—and direct toxicity of these components, occasionally triggered by infectious, inflammatory, and hematological disorders and drugs, among others. In addition, there is a dysregulation of adaptive immunity, including a functional and distribution imbalance of the different subtypes of T and B lymphocytes. MCD has a good response to corticosteroid treatment, especially in pediatric patients, but recurrences are frequent. The natural history of the disease may vary widely, but proteinuria is the cardinal prognosis factor in renal outcome.

Keywords

Nephrotic syndrome · Podocytopathy · Steroid-sensitive · Proteinuria · Relapse

Description of the Disease

Minimal change disease (MCD) is a podocytopathy in which the glomerular filtration barrier is damaged with pedicellar fusion, causing the filtration of molecules that are restricted under physiological conditions, with massive proteinuria and nephrotic syndrome [1]. Characteristically, light microscopy shows a morphologically normal glomerulus, without immunoglobulin or complement deposits in immunofluorescence and with the presence of pedicellar fusion visible by electron microscopy.

It is the main cause of nephrotic syndrome in childhood (up to 90% of cases), with a characteristic age of presentation between 2 and 7 years, being less frequent in adults (10–15%). The global incidence is 0.4–2.4 cases per 100,000 inhabitants/year. MCD has a good response to corticosteroid treatment, especially in pediatric patients, but recurrences are frequent. The response to corticosteroids decreases with age. Overall, the long-term prognosis is favorable, reaching remission rates of up to 90% and a low risk of end-stage renal disease (less than 5% of patients).

Over time, it has been debated whether MCD and focal segmental glomerulosclerosis (FSGS) represent different evolutionary stages of the same disease. Thus, in this case, the progression of cellular damage of the foot processes would be reflected in the transition of the histological pattern. However, this relationship is currently not established and, for the time being, they are described as two different entities.

The pathogenesis of the disease is not entirely clear [2]. It is probably the consequence of the interaction of several factors rather than a single mechanism of injury. Firstly, the contribution of genetic factors, especially the presence of mutations that cause structural or functional abnormalities of genes that encode proteins that constitute the different components of the filtration barrier. These include, among others, the podocyte cytoskeleton, slit diaphragm glycoproteins, the fenestrated endothelium, and glomerular basement mem-

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brane (i.e., NPHS1, NPHS2, ACTN4, etc.). In addition, there is a dysregulation of adaptive immunity, including a functional and distribution imbalance of the different subtypes of T and B lymphocytes [3, 4].

The disease can also be mediated by direct toxicity or mediated by cytokines triggered by infectious processes (respiratory infections, syphilis, tuberculosis, HIV, HBV...), hematological (special mention of Hodgkin's lymphoma but also leukemia), drugs (NSAIDs, antibiotics, bisphosphonates...), vaccines, allergens (milk, eggs, pollen, dust, bites...), systemic inflammatory or autoimmune states (SLE) and, less frequently, neoplasms of solid organs (thymoma, renal cell carcinoma, etc.). It has also been postulated that these processes could mediate the production of a glomerular permeability factor that causes podocyte damage, although this appears to be more common in FSGS [5].

With this damage to the glomerular filtration barrier, there is a dysfunction of the two main mechanisms that restrict the filtration of molecules, which are charge selectivity and size selectivity. In the first case, the high negative charge of the proteins that form this barrier is lost (particularly, but not exclusively, of podocalyxin). Therefore, the sieving coefficient increases, allowing negatively charged proteins, such as albumin, to enter the urinary space. In the second case, structural or functional abnormalities of the proteins expressed in this barrier, and which constitute the filtration diaphragm (nephrin, NEPH1, p-cadherin, podocin or alpha-actin, etc.), alter the mechanism of selectivity of size, also allowing the filtration of large molecules [6].

A greater knowledge of the disease will allow moving from the classical classification of primary and secondary MCD to a classification based on pathogenesis.

Signs and Symptoms

Clinically, MCD manifests as a nephrotic syndrome due to the massive loss of protein in urine (with high proteinuria >3.5 g/24 h, predominantly albumin, which manifests as foamy urine). Consequently, patients present hypercholesterolemia, hypoalbuminemia, edema, and, in many cases, anasarca, with weight gain due to fluid retention. The edema can be found in any location, so there may be pleural and pericardial effusion, and intestinal edema (with nonspecific gastrointestinal manifestations such as nausea, abdominal pain, and even ascites), among others. Blood pressure is usually normal.

Table 98.1 Clinical signs and symptoms

	Children (%)	Adult (%)
Fatigue	>70	>70
Edema	100	100
Anasarca	>80	<60
High blood pressure	<5	40
Arterial thrombosis	1	3
Acute kidney injury	<5	25
Vein thrombosis	2	>25
Infections	>35	<20

The urinary loss of high-molecular-weight proteins such as immunoglobulins confers a greater susceptibility to infections, especially at an early age. Patients with nephrotic syndrome have a prothrombotic state due to a complex imbalance in the activity of procoagulant and anticoagulant proteins and manifest as thrombosis, mainly venous but also arterial (renal veins, lower extremity thrombosis, splanchnic vessels, pulmonary thromboembolism, etc.).

The presence of acute kidney injury is rare, but its incidence increases in elderly patients, and it is generally of functional etiology due to congestion and intravascular depletion and can be aggravated by diuretics. Renal vein thrombosis may be also a cause of acute kidney injury [7]. Finally, persistent protein loss leads to long-term symptoms, such as malnutrition, osteoporosis, and atherosclerosis. The summary of signs and symptoms can be found in Table 98.1 [8, 9].

Laboratory Findings

The main laboratory findings in MCD are proteinuria in the nephrotic range (>3 g/24 h, predominantly albumin, or 40 mg/h/m^2 in children), hypoalbuminemia (<30 g/L), hypercholesterolemia, and hypertriglyceridemia. Other laboratory findings in MCD can be found in Table 98.2. Given the decrease in serum proteins and globulins, there is an increase in the synthesis of hepatic proteins, including lipoproteins and some procoagulant factors, which would partially explain the hypercholesterolemia and high risk of thrombosis in these patients. Furthermore, regarding hypercoagulability, there are other causes that favor clot formation, such as increased platelet aggregation and loss of anticoagulant factors in the urine (such as antithrombin III or plasminogen).

It is noteworthy that, during the study of an adult new-onset nephrotic syndrome, it is recommended to expand the

Table 98.2 Laboratory findings

Urine	
Sediment	Normal (occasionally, mild hematuria)
Proteinuria	Nephrotic range, predominantly albumin

Blood			
Lipid abnormalities		*Protein electrophoresis*	
Cholesterol	↑	Albumin	↓
LDL/VLDL	↑	Gammaglobulins	↓
Triglyceride	↑	IgG	↓
Coagulation		IgM, IgA, IgE	↔↑
aPTT	↓	α-Globulin and β-globulin	↑
Antithrombin III	↓	*Others*	
Factors IX, XI, XII	↓	Vitamin D: 25(OH), 1-25(OH)	↓
Plasma plasminogen	↓	Transferrin	↓
Factors II, V, VI, VIII, X, XIII	↑	Metals: Iron, zinc…	↓
Fibrinogen	↑	C3 and C4	↔

study with other diagnostic tests for diseases that can mimic the clinical picture of a MCD, with an autoimmune profile (ANA, anti-dsDNA, anti-PLA2R, anti-THSA7, etc.), immunofixation in serum and urine, κ:λ free light chain ratio, among others. However, and importantly, the histological findings in these cases will be different from those in MCD.

Diagnostic Criteria

MCD only can be diagnosed in patients with nephrotic syndrome and a renal biopsy with the following features (Table 98.3). Characteristically, light microscopy shows an absence of glomerular lesions, occasionally with minimal focal increase in mesangial cellularity or matrix. Immunofluorescence is negative, with no immune deposits, although occasionally very subtle staining of IgM and C3 deposits is observed in mesangium. There are no specific characteristic tubular, interstitial, or vascular morphological findings, beyond those caused in cases of massive proteinuria. The characteristic findings of the disease are seen on electron microscopy, which demonstrates extensive foot process effacement but no electron-dense deposits [8].

However, in pediatric patients under 12 years of age, the biopsy could be omitted and treatment with steroids can be initiated, assuming that, in the case of good response, the majority of cases of steroid-sensitive nephrotic syndrome at those ages correspond to MCD (and they are referred as *steroid-sensitive nephrotic syndrome*). In these cases, a biopsy will be recommended to rule out other causes in those patients who do not respond to initial treatment with corticosteroids or when another disease is suspected.

Table 98.3 Main findings in renal biopsy in MCD

Renal biopsy	
Ligh microscopy	Glomeruli: absence of lesions. Occasionally, minimal focal increase in mesangial cellularity or matrix
	No specific characteristic tubular, interstitial or vascular morphological findings, beyond those caused in cases of massive proteinuria
Immunofluorescence	Negative
Electron microscopy	Extensive foot process effacement but no electron-dense deposits

Therapy and Prevention

Immunosuppressive Treatment

The treatment of MCD is not the scope of this chapter, but the main therapeutic options deserve a brief mention. There are differences depending on whether the disease occurs in children or adults [9]. In summary, in adults, the KDIGO guidelines [10] recommend a high dose of oral glucocorticoids for initial treatment for a first episode of nephrotic syndrome due to MCD in adults. About 80–90% of patients respond to corticosteroid treatment, most of them during the first 4–6 weeks. The dose of corticosteroids must be tapered 2 weeks after achieving complete remission. There are no studies comparing rapid versus slower glucocorticoid tapering in adults. Usually, they are tapered by 5 to 10 mg per week after remission has been achieved for a total period of glucocorticoid exposure of approximately 24 weeks.

In patients in whom glucocorticoids may be relatively contraindicated or in case of steroid-dependent MCD, treatment with tacrolimus may be considered [11]. Other options are oral cyclophosphamide or mycophenolic acid analogs. These treatments have remission rates (complete and partial) of 90%, 75%, and 75%, respectively. However, the risk of relapse is high after drug withdrawal. Another option is a combination therapy of one of these drugs with low doses of corticosteroids. Finally, KDIGO guidelines include, in addition to the drugs previously mentioned, the consideration of using rituximab for the treatment of frequently relapsing/steroid-dependent MCD, rather than prednisone alone or no treatment [12].

Management of Nephrotic Syndrome

Along with the specific treatment of the disease, the complications of nephrotic syndrome must be addressed: first, optimize antiproteinuric treatment, preferably with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs); achieve optimal control of blood pressure; treat dyslipidemia with statins when necessary; use prophylactic anticoagulation in cases of severe hypoalbuminemia (albumin <20–25 g/L) [13]; and, finally, treat infection prophylaxis, by updating the vaccination schedule, with trimethoprim/sulfamethoxazole and, occasionally, replace with immunoglobulins.

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Focal and Segmental Glomerulosclerosis

99

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Abstract

Primary focal segmental glomerulosclerosis (p-FSGS) is an orphan renal disease in both children and adults, but it is a frequent cause of proteinuria. The secondary form is due to hyperfiltration, which results from increased glomerular capillary pressure, viral infection, or toxin exposure. Primary forms typically do not respond well to corticosteroid treatment and may even be corticosteroid-dependent; in such cases, a combination of calcineurin inhibitors and corticosteroids or rituximab and corticosteroids may be beneficial, but corticosteroid treatment remains the first-line treatment. The primary form often recurs after transplantation.

Keywords

Focal segmental glomerulosclerosis (FSGS) · Nephrotic syndrome · Classifications · Pathophysiology · Prognostic factors · Treatments · Biomarkers · Genetics · Renal transplant

Introduction

Focal segmental glomerulosclerosis (FSGS) is the cause of 10–15% of cases of adult nephrotic syndrome (NS) [1]. It is not a disease but a histological pattern, characterized by effacement and fusion of variable extension of the podocyte and sclerosis affecting part of some glomeruli (segmental and focal lesion). This pattern is not exclusive to this pathology, it can be observed in several pathologies with different pathogenesis, prognosis, and treatment [2].

The Podocytopathies are entities that have a lesion in the podocytes causing proteinuria, the spectrum of this entity includes minimal changes disease (MCD), diffuse mesangial IgM, and FSGS. The lesion may be reversible or, in some cases, may be the cause of Chronic kidney disease (CKD) [2]. On the basis of the pathophysiological mechanisms, a distinction can be made between primary, secondary, and hereditary forms of FSGS [3] (Fig. 99.1).

p-FSGS are of immunological origin. They are caused by one or more unidentified circulating factors or toxic factors [2]. Most respond to immunosuppresive therapy (IS), half of those who undergo Kidney transplant (KT) relapse. Renin-angiotensin aldosterone system inhibitors (RAASI) do not decrease proteinuria in these patients [3].

Secondary FSGS is an adaptive form caused by a reduction in the number of functioning nephrons or by direct podocyte injury from drug toxicity or viral infection [4]. (Table 99.1). Nephroprotective treatment including RAASI and sodium-glucose cotransporter type 2 inhibitors (iSGLT2) usually decreases proteinuria.

Hereditary forms are the result of mutations in more than 60 genes encoding structural and functional proteins of the glomerular filtration barrier (GFB). In children, genetic FSGS accounts for 30% of children with CRNS who have

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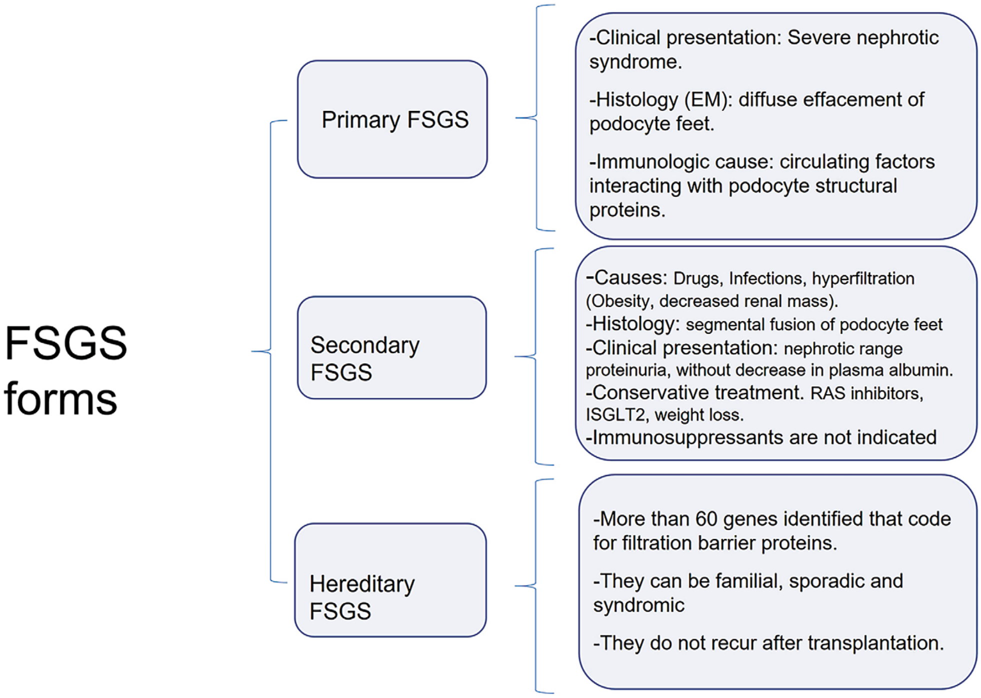
Fig. 99.1 Characteristic of the different FSGS. *FSGS* focal and segmental glomerulosclerosis type, *EM* electron microscope, *RAS* renin-angiotensin system



-Clinical presentation: Severe nephrotic syndrome.

-Histology (EM): diffuse effacement of podocyte feet.

-Immunologic cause: circulating factors interacting with podocyte structural proteins.

-Causes: Drugs, Infections, hyperfiltration (Obesity, decreased renal mass).
-Histology: segmental fusion of podocyte feet
-Clinical presentation: nephrotic range proteinuria, without decrease in plasma albumin.
-Conservative treatment. RAS inhibitors, ISGLT2, weight loss.
-Immunosuppressants are not indicated

-More than 60 genes identified that code for filtration barrier proteins.

-They can be familial, sporadic and syndromic

-They do not recur after transplantation.

Table 99.1 Summary of the most common causes of secondary FSGS

Infectious diseases	HIV, Epstein-Barr-virus, parvovirus B19, CMV, HCV
Drugs/ pharmaceutical products	Anticalcineurin, pamidronate, mTOR inhibitors, anabolic steroids, heroin
Adaptive to the hyperfiltration	Decreased renal mass: renal dysplasia, surgical or functional single kidney
	Without decrease in renal mass: obesity-related FSGS, primary glomerulonephritis, diabetic nephropathy

HIV human immunodeficiency virus, *CMV* cytomegalovirus, *HCV* hepatitis C virus

undergone genetic testing [5], but only 10% of adults, and 40% of these are familial, not sporadic [6]. Furthermore, there is no recurrence of hereditary FSGS after RT [4].

Epidemiology

There is a progresive increase in the incidence of FSGS in the United States, especially in African-American (AA) origen patients [7].

A multicenter study (29 nephrology services) from all over the world included 42,603 patients with glomerular diseases diagnosed in the period 2012–2013. The incidence of FSGS as a cause of NS varies by region: Europe (14.9%), North America (19.1%), Latin America (14.8%), and Asia (6.9%). It is worth noting that patients of European and Asian origin living in the United States have a higher incidence than those living in their continent of origin [8]. In recent decades, the overall incidence of FSGS and its incidence as a cause of NS and CKD have increased in the United States [5].

In Spain, from 1994 to 2019, 26,671 kidney biopsies (KB) were performed, with FSGS accounting for 8% of glomerular diseases [9].

Clinical Presentation

p-FSGS presents with nephrotic syndrome, arterial hypertension, microscopic hematuria, and acute kidney injury (AKI) in 30–45% of cases [3]. AKI is associated with renal ischemia, nephrotoxic drugs, diuretics, and severe hypoalbuminemia [10]. Thrombotic complications occur in more than 20% of cases. FSGS secondary to hyperfiltration does not have hypoalbuminemia at presentation, whether proteinuria is in nephrotic range or not.

Evolution and Prognostic Factors

See definitions in Table 99.2.

Evolution

Response to corticosteroids: 34% to 53% of adults and 10% to 20% of children experience corticosteroid-resistant nephrotic syndrome (CRNS). Of these, 47% to 66% achieve

Table 99.2 Definitions

	Definitions
Nephrotic syndrome	Proteinuria greater than 3.5 g/24 h and plasma albumin less than 30 g/L
Complete remission	Proteinuria less than 0.3 g/24 h or PCR less than 300 mg/g, less than 30 mg/mmol, serum albumin greater than 3.5 g/L and serum creatinine equal to baseline
Partial remission	Proteinuria between 0.3 g–3,5 g/24 h or PCR between 300–3500 mg/g or 30–350 mg/mmol or decrease of more than 50% of the initial proteinuria
Relapse	Proteinuria greater than 3.5 g/24 h or PCR 3500 mg/g, 350 mg/mmol. In case of PR an increase of greater than 50% after reaching PR
Corticosteroid-sensitive nephrotic syndrome	Disappearance of proteinuria and normalization of plasma albumin after corticosteroid therapy
Corticosteroid-resistant nephrotic syndrome	Proteinuria greater than 3.5 g/d or PCR greater than 3.5 mg/g, 350 mg/mmol persistent or a decrease of less than 50% of baseline despite treatment with corticosteroids (prednisone)for 16 weeks at 1 mg/kg/day or 2 mg/kg/48 h.
Corticosteroid-dependent nephrotic syndrome	Corticosteroids-dependent relapse during corticosteroid treatment or during the first 2 weeks after discontinuation of corticosteroid treatment
Frequent relapses of nephrotic syndrome	More than 2 relapses in the first 6 months or more than 3 relapses in 1 year after starting corticosteroid treatment

CR complete remission, *PR* partial remission, *NS* nephrotic syndrome, *CSNS* corticosteroid-sensitive nephrotic syndrome, *CRNS* corticosteroid-resistant nephrotic syndrome, *CDNS* corticodependent nephrotic syndrome, *FRNS* frequent relapsing nephrotic syndrome

complete remission (CR) or partial remission (PR), while 32% to 47% do not [6]. In addition, 45% of CRNS cases do not respond to calcineurin inhibitors (CNI), and 9.5% of these cases experience worsening of renal function during an observation period of 23.6 months (6–65.5). Relapses occur in 30–60% of cases [4].

The disease progresses to CKD in 50% of adults and 30–40% of children within 6–8 years. According to the Scottish renal biopsy registry (2013–2017), 8% of patients under 60 years old, and 25% of those over 60 years old require renal replacement therapy after 3 years of follow-up [4].

Mortality: In the Scottish study mentioned above, individuals under 60 years of age had a mortality risk that was twice as high as that of the general population of the same age during a 3-year follow-up. The primary cause of death was cardiovascular disease, accounting for 28% of deaths compared to 18% in the general population [4].

Prognostic Factors

Remission is a positive prognostic factor regardless of the histological variant or treatment used. Achieving CR or PR results in a renal survival rate of over 95% at 10 years, whereas failure to achieve remission leads to a renal survival rate of less than 30%. Treatment with immunosuppressive drugs (IS) increase the likelihood of achieving remission and decrease the risk of CKD. Early achievement of remission reduces the risk of relapse [11].

Severe tubulointerstitial lesions are a poor prognostic factor in pathology [12].

Pathology

The primary and diagnostic injury is sclerosis that affects a portion of the glomerular ball (segmental) in some glomeruli (focal). It is accompanied by a collapse of the capillary loops, an increase in the mesangial matrix, and condensation in the vascular pole, perihilar, and with a focal lesion of hyalinosis (acellular, smooth, and homogeneous material, fuchsinophilic with trichrome). The Columbia classification is commonly used for subdivide FSGS into five histologic classes: collapsing, cellular, “tip,” perihilar, and “not otherwise specified” (NOS), regardless of whether primary or secondary forms are involved [1, 12].

Ultrastructural study with electron microscopy (EM) is essential to identify possible secondary forms. In primary forms, the fusion of pedicels is diffuse in more than 70% of biopsies, while in secondary forms, it is usually segmental. In hereditary forms, the extent of fusion varies, depending on the gene involved. If the gene encodes cytoskeletal or slit diaphragm proteins, the fusion can be variable, while if it encodes other proteins, it is usually segmental [12].

Pathogenesis and Biomarkers

Currently, there are no biomarkers in serum or urine to diagnose different podocytopathies, differentiate pathophysiological mechanisms, and generate therapeutic targets. However, with the development of new technologies, such as single-cell sequencing, proteomics, and the determination of micro-RNA in serum and urine, it may be possible to determine therapeutic targets. It is important to note that the results of these new technologies still need to be confirmed [13].

Pathophysiological Mechanisms

It is likely that one or more circulating factors are involved in p-FSGS. According to some authors, the same permeability factor(s) could be responsible for both MCD and FSGS [14].

Anti-nephrine antibody were recently discovered in the serum of 30% of patients in a cohort of 62 adults and children with MCD. Plasmapheresis can induce remission of NS and eliminate circulating antibodies [15].

Response to Treatment

Although FSGS and CRNS or MCD and corticosteroids-sensitive nephrotic syndrome (CSNS) are still commonly used interchangeably in the literature, it is important to note that cortico-sensitivity is not synonymous with MCD (10–30% are CR), nor CRNS with FSGS (50% are CSNS) [16].

The podocytopathies classification is based on their pathophysiological mechanism.

FSGS is characterized by an initial injury to the podocyte or another component of the glomerular basement membrane (GBM). The origin of this injury can vary, including circulating factors in primary forms, mutations of genes encoding GFB proteins in genetic forms, and mechanic stress in forms secondary to hyperfiltration.

Primary Forms

The primary forms are caused by one or more circulating factors that are toxic to the podocyte. The secretion of these factors is a result of poorly understood changes in the function of T (TL) and B (BL) lymphocytes. An imbalance between T-helper 17 (TH17) and regulatory T (TH17/Treg) lymphocytes has been reported. The efficacy of anti-CD20 monoclonal antibodies in many cases of corticosteroids-dependent nephrotic syndrome (CDNS) infers the involvement of BL. p-FSGS relapses within hours or days after RT in 30%–50% of patients.

Factors that may contribute to the development and recurrence of FSGS after kidney transplantation (KT) include cardiotrophin-like cytokine factor-1 (CLCF-1), an isoform of ApoA1 (ApoA1b), anti-CD40 antibodies and soluble urokinase receptor (suPAR).

suPAR is the soluble form of the urokinase-type plasminogen activator receptor (soluble urokinase-type plasminogen activator receptor). It activates podocyte beta-3-integrin, which plays an important role in regulating the cytoskeleton and podocyte adhesion to the GBM. In cases of post-RT recurrence, plasma exchanges can decrease plasma suPAR levels, podocyte beta-3-integrin activity, and pedicle fusion. The role of serum levels in differentiating FSGS from other glomerular diseases, as well as primary from secondary forms, is questioned [4, 17]. CLCF1 belongs to the IL-6 family. It is present in the plasma of patients with post-KT recurrence of FSGS. Its role as a permeability factor remains to be confirmed [17].

MicroRNAs are small non-coding RNA molecules (21–23 nucleotides) that regulate gene expression at the posttranscriptional level. They silence or degrade target mRNA. In rats, the expression of miR-193a produces FSGS.

This microRNA inhibits the transcription of the WT1 protein in podocytes, which in turn affects the activation of some genes involved in podocyte function, such as NPHS1. MiR-193a expression is increased in the glomeruli of patients with non-genetic forms of FSGS, but not in healthy subjects or in patients with other glomerular diseases [4, 17].

The recurrence of FSGS after KT is preceded by an increase in the level of anti-CD40 antibodies. They belong to the TNF-receptor superfamily and act as co-stimulatory molecules in immunity. They are expressed in various tissues, including antigen-presenting cells, endothelium, and epithelial cells, such as podocytes, and stimulate the production of chemokines, metalloproteases, suPAR, and uPAR. These are experimental data that require confirmation [4, 17].

There is still no evidence that any of the above candidates may be responsible for permeability.

Hereditary Forms

As mentioned above, approximately 30% of children and 10% of adults with CRNS have a mutation in one of the genes that encode proteins essential for maintaining the structure and/or function of the glomerular filtration barrier (GFB) [18]. Over 60 genes have been identified, including those that are part of the structure or participate in the function of the filtration diaphragm. The following proteins are involved: NPHS2, NPHS1, CD2AP, TRPC6, ACTN4, INF2, MYO1E, ARHGAP24, ANLN, APOL1, WT1, PAX2, COL4A3/4/5/5/6, COQ2, COQ6, PDSS2, COQ8 (ADCK4), MT-TL1, and SCARB2 [4, 18].

An example of a genetic risk variant for FSGS is present in the APOL1 gene. This risk variant is associated with the development of CKD and is found in 35% of the general population of African descent in the United Sates, 26% of the Central African population, and 50% of the West African population. It is worth noting that 40% of patients with CKD due to FSGS are african american (AA) origen [4, 12].

Secondary Forms

In all secondary forms, there is an increase in mechanical stress due to intraglomerular hypertension. This occurs as a compensatory mechanism for the decrease in the number of nephrons, which increases the glomerular filtration rate (GFR) per single nephron to achieve a normal global GFR. These forms typically present with non-nephrotic proteinuria and renal failure. They do not respond to immunosuppressive therapy and progress slowly to CKD [6]. Recurrence after renal transplantation is not observed.

Treatment

Treatment of Primary Forms

Corticosteroids are the first-line treatment. If the treatment lasts less than 16 weeks, only 15% of patients achieve CR or PR. However, if the treatment lasts more than 16 weeks, 61% of patients achieve complete remission [4]. The duration of treatment affects the outcome. Responders have a median treatment duration of 5.7 months [4].

Most authors recommend an initial dose of prednisone 1 mg/kg/d (maximum 80 mg/d) or 2 mg/kg/d every other day (maximum 120 mg) until remission is achieved. However, this dose should not be administered for more than 16 weeks. Steroids should be discontinued if no decrease in proteinuria is observed by week 16. Responders typically experience a decrease in proteinuria between the fourth and eighth weeks.

Once complete remission is achieved, the corticosteroid dose is gradually tapered by 5 mg per week and discontinued 6 months after initiation. The same protocol should be followed in case of recurrence.

CNI are indicated as second-line treatment for CSNS only in cases of frequent relapses, intolerance, or relative contraindication to corticosteroids (such as severe osteoporosis, obesity, diabetes or psychiatric disease). In the latter case, they can be used without corticosteroids from the start.

Cyclosporine A (CsA) works by inhibiting calcineurin, a calcium ion-dependent phosphatase. Calcineurin dephosphorylates NFAT (nuclear factor of activated T cells) transcription factors, allowing their translocation into the nucleus and lymphocyte activation. CNI prevent this phenomenon. Tacrolimus inhibits T-lymphocyte activation by binding to the intracellular protein FKBP2, forming a complex that competitively inhibits calcineurin.

The initial dose of CsA is 3–7 mg/kg/day, divided into two doses, and should be adjusted to reach levels of 100–175 ng/mL [7]. Tacrolimus should be initiated at a dose of 0.05–0.1 mg/kg/day to achieve levels of 5–10 ng/mL. It is recommended to continue treatment for a minimum of 6 months to assess response. The response rate is 47% for complete or partial response. After discontinuation, the risk of relapse is very high (60–80% at 1 year). To prevent relapses, plasma levels are maintained for 12 months if complete or partial response is achieved. Afterward, the dose of CNI is gradually reduced for 12 months until it is discontinued [11].

There have been no studies comparing mofetil mycophenolate (MMF) to corticosteroids. We only have a few observational studies without conclusive results [4].

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen located on the cell surface of the BL. In CDNS, it has been shown to be able to maintain a prolonged remission in children [11].

In a recent multicenter study, 346 children with CDNS received a mean of 3.4 doses of rituximab. The mean follow-up period was 6 years (ranging from 4.3 to 7.7 years). The duration of the remission periods increased with the number of treatments received: the first relapse occurred after 10 months of treatment. In 70% of cases, B cell reconstitution coincided with a relapse (on average 2.6 months later). In the remaining 30% of cases, there was no relapse. Side effects were rare and not serious, including hypogammaglobulinemia (51%), infections (4.5%), and neutropenia (3.7%). At the end of the study period, 96% of children had normal kidney function [4, 16].

Observational, retrospective studies, or studies with few cases included have shown favorable results in adults. The GLOSEN study involved 50 adults with CDNS or frequent relapses, with 28 receiving rituximab and 22 receiving other immunosuppressants as the control group. In the rituximab group, 83% achieved complete remission, compared to 63% in the control group. The rituximab group also had fewer relapses per year and required less immunosuppressant medication to maintain remission [16].

Corticosteroids, CsA, and rituximab directly protect podocytes by stabilizing the actin cytoskeleton. Corticosteroids increase nephrin expression, CsA inhibits synaptopodin dephosphorylation, and rituximab restores the expression of sphingomyelin acid phosphodiesterase 3B (SMPDL3B), which is decreased in FSGS and necessary for proper cytoskeleton function.

Dapaglifozin is a type 2 inhibitor of sodium-glucose cotransporter (SGLT2i) that can reduce glomerular hyperfiltration and provide long-term nephroprotection in various nephropathies, including FSGS [4].

There are still many uncertainties regarding treatment. Clinical trials should accurately classify patients based on the described etiological groups and only use immunosuppressants in primary forms.

Follow-up should be adequate to evaluate the long-term side effects of biologic treatments. In cases of CDNS, it may be worth considering the combination of two immunosuppressants or extending the use of rituximab to prolong remission periods. Different maintenance therapy protocols with rituximab (dose, periodicity, duration) should be compared.

Treatment of Secondary Forms

Whenever possible, the underlying cause should be treated. In cases of obesity, weight loss measures should be implemented. In cases of toxicity, the responsible drug or toxin should be discontinued.

Nephroprotective treatment should follow the same guidelines as for all patients with proteinuria: salt restriction, loop diuretics, and thiazides, if necessary, along with RAASI to strictly control blood pressure. Maximum tolerated doses should be used. Dapaglifozin may be incorporated into nephroprotective treatment if appropriate. General measures such as weight loss and exercise are also important [4]. IS treatment is not indicated in secondary forms.

Relapse After RT of the Primary Forms

Recurrence of FSGS only occurs in primary forms. It occurs in 30 to 60% of patients after the first transplant and in 80% to 100% after a second transplant, in case of recurrence in the first one. It may occur immediately in some cases, generally during the first few weeks after the transplant. The risk of graft loss after recurrence is 40–60% [1, 4].

The primary risk factors for recurrence are disease onset at a young age, rapid progression (less than 3 years) from initial disease to stage 5 CKD, previous nephrectomy of the kidney themselves, and relapse in a previous RT [19].

As previously mentioned, relapse is caused by a circulating factor. Most groups treat relapse by using plasma exchanges, with or without rituximab. If the relapse occurs within 3 months, plasma exchanges should be initiated immediately to achieve a CR or PR in 60–75% of cases [19].

If there is no response to plasma exchange with or without rituximab, alternative treatment have been used. However, their efficacy remains to be confirmed.

Despite treatment, graft survival is low, at 52–61% after 5 years [20].

Conclusion

FSGS is a histologic pattern that corresponds to several diseases with distinct etiologies, pathophysiologic mechanisms, and treatments.

Prior to treatment, it is necessary to make a differential diagnosis between these diseases, including primary, secondary, and genetic forms. This requires a full history and physical examination; pathological study, in some cases EM if available; and, in some cases, genetic study.

Hereditary forms are often undiagnosed. The true prevalence of forms with autoantibodies remains to be seen in the future.

Immunosuppressants should only be used to treat primary forms.

Our understanding of NS is constantly improving, and this information will enable a classification based on pathophysiological mechanisms, with specific therapeutic targets.

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Membranoproliferative Glomerulonephritis

100

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Abstract

Membranoproliferative glomerulonephritis (MPGN), also known as mesangiocapillary glomerulonephritis, is a complex and rare cause of glomerular disease. Its name describes the main pathological features of this entity: thickening of the glomerular basement membrane due to the deposition of immune complexes and cellular proliferation caused by the influx of mesangial cells and inflammatory cells, mainly monocytes. Thus, MPGN is not a clinical entity per se but rather the pathological expression of different clinical processes. This finding should prompt clinicians to search for a possible underlying etiology. New classifications based on pathophysiology and immune deposition on renal biopsy are now accepted. MPGN accounts for 4–5% of all glomerular diseases. The prognosis is usually poor, with an estimated renal survival of 60–65% at 10–15 years after initial renal biopsy, regardless of treatment. Signs of prognostic value are as follows: nephrotic syndrome, renal failure, arterial hypertension, crescents, and tubulointerstitial involvement on biopsy. Corticosteroids are the only treatment that has shown a prognostic improvement in this disease in children, but not in adults. Recently, treatment with mycophenolate or rituximab has been associated with an improvement in prognosis.

Keywords

Mesangial proliferation · Immune deposition · Complement antibodies · Nephritic factors · Complement dysregulation · Pathophysiology · New classifications

Introduction

Membranoproliferative Glomerulonephritis (MPGN) is caused by an abnormal immune response, with antibody deposits in the kidneys, leading to chronic inflammation and eventually end-stage renal disease. MPGN is a pathological definition of a very complex entity. (1) immune deposits in various structures of the glomerular basement membrane, (2) intense glomerular hypercellularity due to mesangial proliferation involving cells and matrix with interposition of mesangial cells in the capillary wall, and (3) influx of inflammatory cells, mainly monocytes [1]. Classifications based on pathogenesis are currently accepted.

Epidemiology

MPGN is a glomerulonephritis with a chronic course in the majority of cases that is more common in children and young adults, with a incidence between the ages of 5 and 15, although it can be diagnosed at any age. Some studies suggest a slightly higher incidence in males, but in most studies, the sex ratio is close to one. Its overall incidence is gradually decreasing in developed countries and accounts for approximately 7–12% of glomerular diseases diagnosed by renal

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biopsy. It still accounts for a high proportion of glomerulopathies in underdeveloped or developing countries. The true incidence is difficult to determine because renal biopsy is required for diagnosis, and this procedure is not routinely available in most underdeveloped areas [1, 2].

Clinical Manifestations

It affects both children and adults, although DDD (dense deposits disease) is more common in children and monoclonal gammopathy must be excluded in adults. The clinical features of the disease are variable. Twenty to thirty percent have an asymptomatic course with minimal persistent hematuria and non-nephrotic proteinuria detected in a screening program. Nephrotic Syndrome is present in approximately 50% of cases, ranging from 24% to 69%; hypertension is present in approximately 40%; and renal function impairment at presentation is highly variable, ranging from 15% to 44%, as summarized in Table 100.1.

Table 100.1 Symptoms and signs of MPGN presentation

Symptoms and signs	%
Abnormalities of urine sediment (hematuria and non-nephrotic proteinuria)	20–30
Nephrotic syndrome	50 (24–69)
Acute nephritic syndrome	16–30
Renal dysfunction	15–40
High blood pressure	40
Recurrent episodes of gross hematuria	10–20

The percentages presented come from data from several publications [3, 4] by 7 different authors and a total of 342 patients

Pathogenesis

Based on the new classification, the formation of immune complexes that activate the classical complement pathway may be the mechanism involved in most cases of type I immune-mediated MPGN, but the antigen or antigens that trigger this immune response remain unknown in most cases, and the relationship with hematological diseases, such as monoclonal gammapathy, infections, autoimmune diseases, and others, has not been elucidated. It is difficult to establish a cause-and-effect relationship because neither complement levels nor the presence of C3 nephritic factor (C3Nef) is associated with disease severity or outcome. In MPGN type II and III, alteration of the alternative pathway is due to the presence of autoantibodies to C3 convertase, which stabilize the enzyme to resist inactivation by factor H. In addition, the stability of the convertase is greater than that produced by binding to properdin and is independent of properdin. Another mechanism is the absence or genetic dysfunction of factor H and other regulators of the alternative complement pathway. Some cases of type III MPGN have been associated with a circulating properdin-dependent nephritic factor that affects the terminal loop of the alternative alternative pathway [3, 5, 6]. Clinical data, complement pattern, and histology may help to elucidate the etiology and risk of end-stage kidney disease (ESKD) in MPGN [3] (see Table 100.2).

Table 100.2 MPGN physiopathology and related etiology

Immunocomplex-mediated				Complement mediated	Without deposits
Chronic Infection	Autoimmune disease	Malignant neoplasm	Paraproteins deposition diseases	(genes or antibodies)	TMA (thrombotic Microangiopathy)
Hepatitis C and B virus	Systemic lupus erythematosus (SLE)	Lymphoma	Waldenström’s macroglobulinemia	Anti-CFH, anti-CBF anti-C3, anti-properdin	Kidney transplant glomerulopathy
Endocarditis infected shunt	Sjögren syndrome	Leukemia	Myeloma	C3 Nef (>frequent) C4 Nef (<frequent)	Radiation nephropathy
Leprosy	Cryoglobulinemia	Neoplasm	Monoclonal gammopathy of renal significance	CFH	Antiphospholipid syndrome
Protozoa: Malaria, schistosomiasis		Hydatidiform mole	Fibrillary glomerulopathy	C3	Sickle cell anemia
Mycoplasma			Immunotactoid glomerulopathy		Polycythemia

Summarize the causes related to the pathophysiology of MPGN: membranoproliferative glomerulonephritis, immune complex mediated, complement mediated and without immune deposits

Pathology

MPGN is the most common histologic pattern in C3N and is immunocomplex mediated. Currently, the classification of MPGN into three pathological types based on pathophysiological differences defined by the type and location of deposits detected by immunohistochemistry is accepted [4].

Type I: Mainly presence of subendothelial deposits; subepithelial "hump-shaped" deposits in 15–20% of cases. Mesangial cell proliferation and matrix expansion, and in some cases exudative leukocytes, cause interposition along the membrane, giving the morphological appearance of a "double contour." Matrix expansion and cellular proliferation may be prominent, resulting in a lobular appearance (Fig. 100.1). The composition and distribution of the deposits is variable: C3 is almost always present, C4 and C1q in 50% of cases, and IgG and IgM in 1/3 of cases. The deposits have a granular appearance [1]. When immunoglobulin and complement deposits are of equal magnitude, the diagnosis is immunocomplex-mediated MPGN. When C3 deposits are predominant (increase of at least two magnitudes) or present alone, the diagnosis is C3G [4].

Type II: Also known as DDD, this is characterized by homogeneous dense deposits along the basement membrane and in the mesangium. They also involve Bowman's capsule and tubular basement membrane. C3 immune deposits are described as ribbon-like, linear or sublinear, granular or nodular [6].

Type III: Can be only distinguished from type I by the subepithelial deposits, which are always present in type III, and by the complement pattern. The characteristic lesion of type III MPGN consists of interruptions of the dense lamina associated with subendothelial and subepithelial deposits, sometimes confluent, and combined with multiple layers of newly formed membrane [7].

Serological Characteristics

C3 hypocomplementemia is a characteristic feature but not necessary for diagnosis. The presence of nephritic factor is the most important serological feature of this disease. In MPGN type I, three different patterns of complement activation may be present: (1) Nephritic factor amplification loop (NFa) in this case, C3 is very low and the preceding components of the complement cascade are normal. (2) Nephritic factor of the terminal pathway (NFt), characterized by a decrease in the last complement component (C5–C9); C3 is low to a variable degree and properdin is also decreased. (3) The last and most common pattern is activation of the classical immune complex-mediated pathway with decreased C1q, C2 to a variable degree. The complement pattern of MPGN type III is that of the terminal pathway described above. MPGN type II is characterized by low C3 and the presence of nephritic factor C3 in 80% of cases; antinuclear antibodies (ANA) rheumatoid factor, viral serology for HBV, and HCV should be investigated, but these are negative in primary forms of the disease. Genetic mutations should be investigated in C3 or C3 dominant deposits regardless of histological morphology [3, 8, 9].

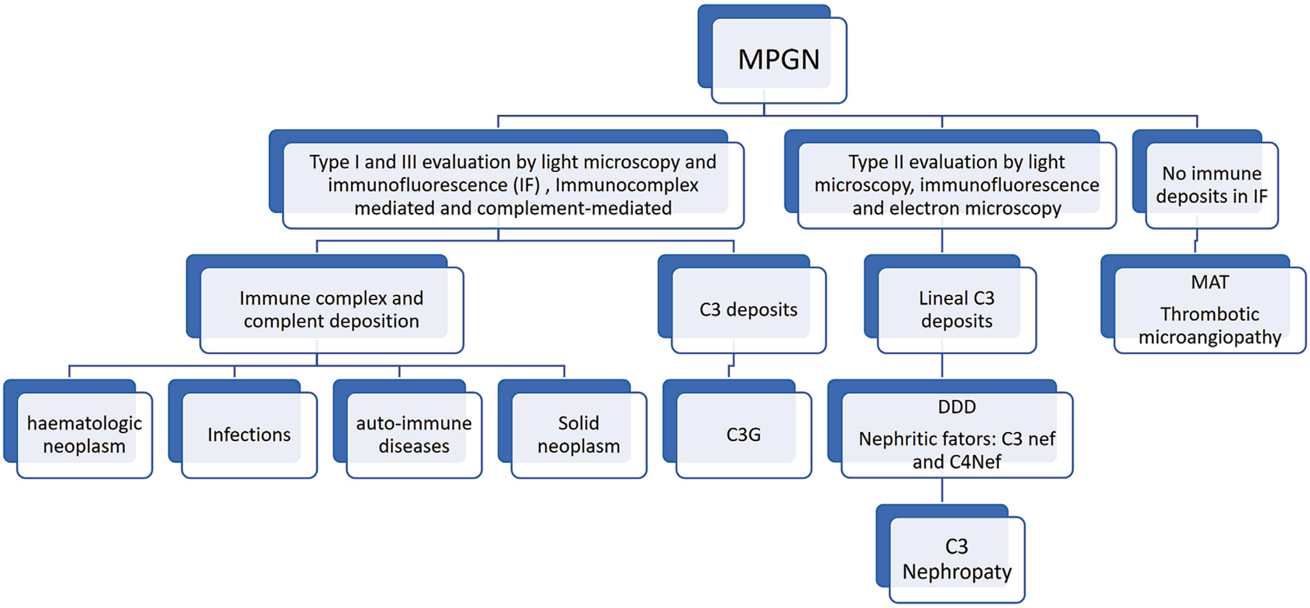
MPGN
Type I and III evaluation by light microscopy and immunofluorescence (IF) , Immunocomplex mediated and complement-mediated
Type II evaluation by light microscopy, immunofluorescence and electron microscopy
No immune deposits in IF
Immune complex and complent deposition
C3 deposits
Lineal C3 deposits
MAT
Thrombotic microangiopathy
haematologic neoplasm
Infections
auto-immune diseases
Solid neoplasm
C3G
DDD
Nephritic fators: C3 nef and C4Nef
C3 Nephropaty

Fig. 100.1 Physiopathology based MPGN classification

Diagnostic Criteria

There are no clinical criteria for diagnosis and the clinical presentation is variable. For the diagnosis and prognostic significance, some histological criteria must be fulfilled, namely, the presence of (1) MPGN morphology (diffuse or segmental thickening of the glomerular membrane and hypercellularity, mainly due to mesangial proliferation), (2) leukocyte infiltration, (3, 4). fibrinoid necrosis, and (5) interstitial inflammation [10, 11].

Treatment

The low incidence of this disease makes it very difficult to design clinical trials of new immunosuppressive and complement-targeting agents. Most randomized trials were conducted in the 1980s and are now outdated. In children, treatment with corticosteroids and/or immunosuppressants have been shown to be better than no treatment. In children with impaired renal function, with or without nephrotic proteinuria, treatment with high-dose prednisone (40 mg/m^2 every other day for 6–12 months) has been advocated [12]. Based on recent studies, the KDIGO guidelines (20–21) suggest that in the absence of a monoclonal gammapathy, C3G in patients with moderate disease should be treated initially with mycophenolate mofetil (MMF) plus glucocorticoids, and if this fails, eculizumab should be considered. In adults [13], treatment of the underlying cause is the treatment of choice; if the cause cannot be identified, rituximab, mycophenolate, or complement-targeting agents may be used, but there is insufficient evidence at present, although clinical trials are ongoing [13]. There are no clinical criteria for diagnosis, and clinical presentation is variable. For the diagnosis and prognostic significance, some histological criteria must be fulfilled, namely, the presence of (1) MPGN morphology (diffuse or segmental thickening of the glomerular membrane and hypercellularity, mainly due to mesangial proliferation), (2) leukocyte infiltration, (3, 4) fibrinoid crecrosis and (5) interstitial inflammation [10, 11].

Prognosis

The long-term prognosis of this disease is poor, as confirmed by most of the studies carried out to analyze its evolution. Renal survival is variable, but large series estimate a mean survival of 60–65% at 10 years with or without treatment, the worst prognostic features being the following: nephrotic syndrome, renal failure at presentation, and interstitial fibrosis [6, 10, 11, 14]; patients with normal interstitial space remain with normal or slightly altered renal function in 63% of cases, and this proportion decreases to 13–25%, when interstitial fibrosis or renal failure is present. The degree of glomerular involvement does not worsen the prognosis but, as in most nephropathies, the presence of crescents on biopsy reduces the likelihood of preserving renal function. Eighty-seven percent of these patients require dialysis or kidney transplantation or die of renal causes [15]. The recurrence rate after transplantation is approximately 30% in MPGN but is highly variable depending on the series, ranging from 9% to 53% [7]. After the recognition of C3G and the increase in renal biopsy for the diagnosis of glomerular involvement at transplantation, the posttransplant recurrence of this entity is estimated to be 62–84%, although graft loss after recurrence varies between 41 and 50%. Recurrence of DDD is difficult to estimate and varies from 18 to 100% depending on the series; a recent report estimates in 40% of patients, but it is the cause of graft loss in less than 10% [15–17].

Conclusions

MPGN is not a disease but a histopathological pattern that has recently advanced in its pathophysiology and classification, determining that the most important factor involved is the activity of the complement system, including those forms mediated by immunocomplexes. This knowledge has led to clinical trials directed at this type of glomerulonephritis, which may drastically change the natural history of this glomerulonephritis in the near future.

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Acute Tubulointerstitial Nephritis

101

Marc Xipell and Luis F. Quintana

Abstract

Acute tubulointerstitial nephritis (ATIN) is characterized by inflammatory infiltrates and edema in the interstitial compartment, usually accompanied by tubular damage. It is frequently associated with acute or subacute renal failure, accounting for up to 10% of all renal biopsies. Drugs are the main cause, especially antibiotics, but other processes such as autoimmune and systemic diseases, infections or metabolic diseases can be a cause of ATIN. The definitive diagnosis of ATIN is provided by the histological study of a kidney biopsy. Treatment requires discontinuation of the causative agent. Although ATIN may resolve spontaneously, a short-term therapeutic regimen with corticosteroids is recommended to reduce the risk of chronic kidney disease.

Keywords

Acute kidney injury · Tubulointerstitial disease · Immune-checkpoint inhibitors · Interstitial fibrosis · Tubular atrophy · Drug induced · Steroid therapy · Chronic kidney disease

Description of the Disease

Acute tubulointerstitial nephritis (ATIN) is a type of kidney injury characterized by inflammatory infiltrates and edema in the interstitial compartment, usually accompanied by tubular damage [1]. It is frequently associated with acute or subacute kidney dysfunction [2–4]. It accounts for between 1–10% of all kidney biopsies, reaching up to 20% when the biopsy is performed for acute renal injury [5–7]. The pathogenic mechanisms are multiple and include, briefly, immune responses against antigens-haptens of tubular epithelial cells, cross-reactivity in shared or similar epitopes, antigen-antibody complex formation and deposition, immune responses on apoptotic cells and also loss of immunological tolerance to endogenous antigens [8–10].

The causes of ATIN are listed in Table 101.1, with drugs being the main cause, especially antibiotics [1, 11–14]. Potentially, any drug can develop ATIN [6]. In these cases it is usually an idiosyncratic hypersensitivity reaction (dose independent). Depending on the pathogenesis and the pharmacological group, there is a different latency period until the appearance of symptoms, which can develop from 7 to 10 days after exposure (such as some antibiotics) to weeks (e.g., allopurinol) and even months (such as proton pump inhibitors and checkpoint inhibitors) [15].

The second main group is immune and systemic diseases [16]. The pathogenesis of ATIN within these diseases is heterogeneous and includes the production of autoantibodies, the deposition of immune complexes in the interstitium and the activation of inflammatory pathways. Finally, regarding ATIN in the context of infectious processes, there is a direct cytopathic effect of microorganisms and the release of proinflammatory cytokines that induce kidney damage.

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Table 101.1 Main causes of acute tubulointerstitial nephritis

Drugs (70–75%)	Antibiotics (30–35%) (penicillins, cephalosporins, quinolones, sulfonamides, macrolides, clindamycin, aminoglycosides, etc.), antiretrovirals (abacavir, acyclovir, foscarnet), NSAIDs, PPIs and H2 antagonists, check-point inhibitors (atezolizumab, ipilimumab, nivolumab, pembrolizumab), tyrosine-kinase inhibitors (sorafenib, sunitinib), diuretics (thiazides, furosemide, torasemide, amiloride, triamterene), ACEIs/ARB II, anticonvulsants (carbamazepine, lamotrigine, levetiracetam, valproate), allopurinol, atorvastatin, gemfibrozil, metamizole, etc.
Autoimmune and systemic diseases (10–20%)	Sjögren syndrome, sarcoidosis, IgG4 disease, systemic lupus erythematosus, tubulointerstitial nephritis and uveitis syndrome (TINU), vasculitis, lymphoproliferative diseases, paraproteinemias, inflammatory bowel disease, atheroembolic disease, DRESS syndrome, etc.
Infections (5–10%)	Brucella, Campylobacter, Legionella, Salmonella, Streptococcus, Mycoplasma, Mycobacterium, Histoplasma, Leptospira, Candida, Toxoplasma, CMV, EBV, hepatitis, HIV, BK virus, etc.
Metabolic diseases (<5%)	Acute nephropathy due to oxalate, urate deposition or acute nephrocalcinosis

Signs and Symptoms

In most cases, symptoms are nonspecific and include general malaise, nausea or vomiting, arthralgias and myalgias [1]. The classic triad of fever, rash, and eosinophilia occurs in less than 10% of patients [17], and is more associated with hypersensitivity reactions, especially when antibiotics are involved [2]. If classified separately, rash is seen only in 15% of cases (usually presenting as maculopapular rash, erythroderma or toxic epidermal necrolysis) and fever and eosinophilia can be found in 27% and 23% of patients, respectively.

From the renal point of view, it manifests as acute or subacute kidney dysfunction and low-grade proteinuria. Urinary sediment may be associated—but not necessarily—with leukocyturia and hematuria. Eosinophiluria has a low sensitivity and specificity (30 and 68%, respectively). Proteinuria is of tubular origin and is usually in the non-nephrotic range. Patients generally have preserved diuresis or there is even polyuria and nocturia due a deficit in urine concentrating capacity of the tubulointerstitial compartment (hyposthenuria). Other affected tubular functions can cause tubular acidosis, glycosuria, phosphaturia, and aminoaciduria (Fanconi syndrome), but this is most common in cases of chronic tubulointerstitial nephritis. The presence of edema or arterial hypertension is rare. In more severe cases, although rare, when there is high inflammation and edema, renal flank pain may occur, reflecting distension of the renal capsule, with oliguria or anuria (Table 101.2).

Its course is usually limited, as long as the cause is diagnosed promptly and treated appropriately, with drug withdrawal when this is involved. Otherwise, persistence of acute inflammation may progress to interstitial fibrosis and chronic kidney disease.

Table 101.2 Main clinical findings in ATIN

Systemic symptoms
General malaise
Nausea, vomiting
Arthralgias and myalgias
Cutaneous rash
Fever
Renal symptoms
Acute or sub-acute kidney dysfunction
Low-grade proteinuria
Leukocyturia and hematuria
Tubular dysfunction: metabolic acidosis, glycosuria, phosphaturia, etc.
Hyposthenuria
Preserved diuresis or polyuria

Laboratory Findings

Blood tests include creatinine, BUN, blood count, ESR, C-reactive protein. A urinalysis is performed with urinary sediment (leukocyturia, eosinophiluria and hematuria may be present). Urine shows low-grade proteinuria, with predominance of tubular proteins on the urinary proteinogram. It is recommended to perform a renal ultrasound, in order to rule out urinary obstruction and also to assess indirect signs of severe inflammation, such as increased kidney size. Other tests are performed according the clinical suspicion of the etiology, with screening for underlying infections or systemic diseases (infectious serology, cultures, Ziehl-Neelsen staining of urine, autoimmunity, proteinogram and immunofixation in serum and urine, etc.), among others.

Table 101.3 Main pathology findings in ATIN

Renal pathology findings
Interstitial edema
Inflammatory interstitial infiltrate
Tubulitis
Acute tubular necrosis

Diagnostic Criteria

The definitive diagnosis of ATIN is provided by the histological assessment of a kidney biopsy [4, 18]. Different findings can be observed depending on the etiology and mechanism of injury. The presence of interstitial edema is characteristic, with inflammatory interstitial infiltrate, predominantly mononuclear cells with monocytes and lymphocytes. Other inflammatory cells such as eosinophils, plasma cells, neutrophils and macrophages can also be observed. The renal tubular epithelium may present focal or diffuse damage, which is associated with acute tubular necrosis and, in some cases, tubular inflammation (tubulitis) (Table 101.3).

The presence of granulomatous lesions with aggregates of giant cells has been more frequently associated with specific drugs (allopurinol), autoimmune diseases (sarcoidosis, Sjögren's syndrome, granulomatosis with polyangiitis, inflammatory bowel disease) or infections (tuberculosis, histoplasmosis, candidiasis, toxoplasmosis). Depending on the suspected etiology, tissue-specific studies will be performed (e.g., immunohistochemistry staining in case of infectious diseases, for detection of cytomegalovirus, adenovirus, BK virus; tissue cultures, etc.). The immunofluorescence study is usually negative, but it can help in some systemic and autoimmune diseases.

Therapy

Treatment of ATIN requires identifying the underlying etiology. When it is secondary to drugs, the identification of the causal agent is not always an easy task, especially in patients with polypharmacy and in cases where the temporal relationship is not so evident.

The likelihood of spontaneous recovery of renal function after discontinuation of the causative agent of ATIN will depend on the time of exposure [17]. Although the possible therapeutic benefit of immunosuppression in cases of ATIN has not been evaluated in prospective clinical trials, different observational studies have found that early treatment with corticosteroids is associated with a greater probability of recovery of renal function [7, 12, 19, 20]. When ATIN is secondary to infections or autoimmune diseases, treatment should be directed to the specific etiology.

The scientific evidence regarding corticosteroid treatment regimen in ATIN is scarce, but if there are no formal contraindications (e.g., an active infection) and the ATIN does not resolve spontaneously, the therapeutic regimen will be aimed at early initiation of high doses of corticosteroids for approximately 2 weeks, with a progressive withdrawal in another 4—6 weeks. As a general rule, the total duration of the treatment should not extend much beyond 8 weeks.

An example of a treatment regimen to use is:

- Pulses of methylprednisolone 125–250 mg/day for 3 days, followed by.
- Oral prednisone at an approximate dose of 0.5 mg/kg/day starting on the fourth day, for 1–2 weeks.
- Subsequently, progressive withdrawal until completing 4–6 weeks of treatment. However, earlier discontinuation of steroid treatment should be considered if no improvement is observed after 2 weeks, in order to avoid adverse effects.

However, the casuistry has some gray areas, since occasionally the causative drug cannot be easily discontinued (e.g., immunotherapy in patients with cancer).

Follow-Up

The prognosis of ATIN is variable, but up to 50% of drug-related cases have incomplete recovery of renal function, especially with NSAIDs or in those cases where exposure has been prolonged (>3 weeks). Likewise, extensive tubulointerstitial fibrosis and atrophy on biopsy are associated with a worse prognosis. The renal prognosis of ATIN in the setting of other systemic diseases is less known.

Patients should be monitored closely during tapering of corticosteroid, to ensure there is no worsening of kidney function. Patients who, at the end of treatment, present complete resolution, with normal kidney function, without proteinuria and with normal urinary sediment, may be discharged from follow-up. Those patients who remain with some grade of chronic kidney disease should be treated depending on the stage of kidney disease.

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Atypical Hemolytic Uremic Syndrome

102

Miquel Blasco Pelicano

Abstract

Clinicians should suspect thrombotic microangiopathy (TMA) in front of microangiopathic hemolytic anemia, thrombocytopenia (or platelet consumption), and organ damage. Atypical hemolytic uremic syndrome (aHUS) is an ultra-rare but devastating form of TMA. aHUS diagnosis is very complicated given its variable clinical presentation (multi-system involvement) and the absence of laboratory tests that allow its inclusive identification (clinical diagnosis by exclusion of all other TMA forms). The endothelial damage that trigger TMA in aHUS patients is mediated by a dysregulation of the alternative complement pathway. Acquired (15% of cases, due to antibodies against factor-H) or inherited, 40–60% of cases present genetic variants in complement genes. Gold standard treatment consists of early introduction of terminal complement blockade (monoclonal antibodies against C5 molecule).

Keywords

Alternative complement pathway · Atypical hemolytic uremic syndrome · Complement system · Endothelial damage · Microangiopathic hemolytic anemia · Thrombocytopenia · Systemic organ damage · Thrombotic microangiopathies

Description of the Disease

Hemolytic uremic syndrome (HUS) was first described by Gasser et al. in 1955 as a clinical entity characterized by thrombocytopenia, hemolytic anemia, and kidney failure [1]. Since then, the spectrum of thrombotic microangiopathies (TMA)—pathological lesion characterized by the existence of thrombi inside arterioles and/or capillaries, usually affecting multiple organs—has evolved from syndromic descriptions to an etiological perspective/classification. An accurate diagnostic approach is crucial given the important therapeutic development of the last decades.

Atypical Hemolytic Uremic Syndrome (aHUS) is an ultra-rare but devastating form of TMA, caused by an overactivation/dysregulation of the alternative complement pathway over the endothelial cells, especially in the kidney [2]. In the past, the term "atypical" HUS was used to describe HUS not caused by the infection of Shiga-toxin *Escherichia coli* (STEC-HUS or typical HUS). Despite TMA classification remaining controversial, in this chapter the term aHUS will be used to define patients with endothelial damage due to alternative complement dysregulation (acquired or inherited), excluding secondary TMA forms.

aHUS onset can occur at any time, however it occurs most often in children (60%) and young adults [3]. There are no significant differences between genders, but when the disease appears in adulthood it has a greater preference for women, especially in the post-partum period [4]. aHUS is considered an ultra-rare disease, with an estimated incidence of 1–2 cases per million inhabitants/year [5]. Without an etiological treatment (terminal complement blockade), aHUS is a systemic and severe disease, leading to end-stage kidney disease (ESKD) in up to 2 out 3 affected patients, 1 year after the onset of the disease [6].

The endothelial lesion that causes TMA in aHUS patients is mediated by a dysregulation of the alternative complement pathway (part of the innate immune system) as a result of genetic predisposition or acquired forms. Approximately between 40–60% of cases of patients with a clinical diagno-

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sis of aHUS carry pathogenic variants and/or risk polymorphisms in genes encoding complement proteins [7], either by a loss/decreased activity of regulatory proteins (*CFH*, *CFI*, *MCP*), or by an abnormally high activity of C3-convertase (gain of function; *C3* and *CFB*). Acquired forms occur in the presence of auto-antibodies against factor-H (5–10% of aHUS patients), resulting in CFH function deficiency [8].

Despite important advances in pathophysiological knowledge and its treatment, detection of aHUS patients remains extremely complicated, since there are no laboratory tests that allow an inclusive diagnosis. It is therefore necessary to exclude all TMA forms until reaching the clinical diagnosis of aHUS. A multidisciplinary evaluation in centers of excellence will be of vital importance to establish an accurate diagnosis that allows the introduction of early targeted therapies (blockade of the terminal complement), changing its devastating natural history (high morbidity and mortality reduction).

Clinical Findings

In most cases, aHUS presentation is acute and severe, with approximately 90% of patients showing a coexistence of microangiopathic hemolytic anemia (non-immune), thrombocytopenia (or platelet consumption), and multi-organ damage [9]. The kidney is the main organ affected [10]; nevertheless, extra renal manifestations are not uncommon (10–45% of cases) (see Table 102.1).

Table 102.1 Signs and symptoms

Organ involvement	Signs and symptoms
Renal (80–90%)	Acute kidney injury, chronic kidney failure, proteinuria, hematuria, high blood pressure [11]
Cardiovascular (35–45%)	Hypertension, myocardial infarction, heart failure, stenosing vascular lesions [12]
Central nervous system (30–40%)	Confusion, facial paralysis, dysarthria, aphasia, dysphagia, altered level of consciousness, psychomotor agitation, seizures, stroke, coma [13]
Gastrointestinal (30–35%)	Diarrhea, abdominal pain, vomiting, pancreatitis, diabetes mellitus, intestinal ischemia, hepatitis [14]
Lung (10–20%)	Dyspnea, acute pulmonary edema, alveolar hemorrhage [15]
Others	Ocular involvement [16], adrenal insufficiency, peripheral vascular disease, skin involvement

References: [11–16]

Laboratory Findings and Serological Markers

Unlike other TMA forms—such as thrombotic thrombocytopenic purpura (TTP) with ADAMTS-13 activity <5–10%—aHUS does not have a laboratory test for an inclusive diagnosis. In case of microangiopathic hemolytic anemia, thrombocytopenia, or organ damage, it will be necessary to exclude all TMA causes until one achieves the clinical diagnosis of aHUS (or complement-mediated TMA).

However, in up to 15% of cases (especially in adolescents), the presence of anti-FH antibodies can be found, which would facilitate a diagnosis of acquired forms of aHUS (Table 102.2). With regard to genetic predisposition, the genetic study should never delay the clinical diagnosis and, above all, the introduction of targeted therapies. However, it is mandatory to carry out a complete genetic study in all patients with clinical aHUS suspicion, since it will provide prognostic information of vital importance to guide the duration of treatment or the risk of recurrence, among others (Table 102.2).

Table 102.2 Laboratory findings and approach in aHUS (autoimmune and genetic forms)

Autoimmune aHUS forms (15%)	aHUS with genetic predisposition (40–60%)
Autoimmune form of HUS, affecting mainly adolescents	Complement genetics may provide the proof of a link between complement dysregulation and disease
Anti–factor H antibodies are mostly IgG; IgM auto-antibodies have also been reported	Candidate genes in aHUS should include: *CFH, CD46, CFI, C3, CFB, and diacylglycerol kinase ε* (*DGKε*) genes
The occurrence of anti–factor H antibodies is associated with a homozygous deletion of the genes encoding *CFH-related protein 1* and *3*	The recommended studies include: a combination of next-generation sequencing panel and multiplex ligation–dependent probe amplification to allow for the identification of large deletions, hybrid genes, or other complex genomic rearrangements
Management approaches include: plasma exchanges, especially in cases of severe extrarenal manifestations (cardiac or neurological); immuno- suppressive drugs (rituximab, cyclophosphamide, or mycophenolate mofetil); and C5 blockade	C5 blockade is actually the gold standard therapy for aHUS
Reference: [8]	Reference: [17]

Diagnostic Criteria

Currently, there are no validated diagnostic criteria that allow an inclusive diagnosis of aHUS. The following table (Table 102.3) shows the main clinical entities that must be ruled out when there is clinical suspicion or histological confirmation of TMA, until the diagnosis—by exclusion—of aHUS is reached.

Despite the absence of validated laboratory tests for an inclusive diagnosis of aHUS, the development of biomarkers to monitor complement overactivation has been increasing in recent decades (Table 102.4). A special mention is required for functional analyses, although they must overcome their current limitations (requires duplication and standardization) to be accepted as diagnostic techniques for patients with aHUS.

Table 102.3 TMA forms [18]

TMA forms	Diagnostic criteria (if available)
TTP or ADAMTS-13 deficiency	– ADAMTS-13 activity <5–10% (90% due to antibodies, 10% genetic variants) – If not available the PLASMIC and FRENCH score could help in the clinical suspicion
TMA associated with infections: STEC-HUS (“typical” HUS) Other infections: Shigella, Campylobacter, Pneumococcus, HIV, parvovirus B19, BK virus, EBV, CMV, Sars-CoV-2, etc.	– Perform cultures and serological determinations according to clinical suspicion
TMA associated with autoimmune diseases: SLE AFS Scleroderma	– Autoimmune panel: ANA; ds-DNA; Anti-nuclear Ag antibodies (Sm, SSA, SSB and RNP); C3, C4 and CH50 levels; antitopoisomerase I antibody (antiScl-70), anticentromere antibody (ACA) and anti-RNA polymerase III antibodies; and anticardiolipin, anti-b2GP-1, and lupus anticoagulant
TMA associated with pregnancy: Pre-eclampsia Eclampsia HELLP syndrome	– Despite its clinical diagnosis, the measurement of the placental growth factor (PlGF) and the soluble fms-like tyrosine kinase receptor-1 (sFlt-1) may be useful in its differential diagnosis with other entities
TMA associated with transplant: Bone marrow transplant Solid organ	– In hematopoietic stem cell transplantation, the most frequent causes of TMA are graft-versus-host disease; opportunistic infections, and pharmacological treatments – In the solid organ TMA is usually associated with rejection, infections, and immunosuppressants
TMA associated with drugs: Cytotoxic agents Endothelial growth factor (VEGF) inhibitors Proteasome inhibitors Immunosuppressants Biological agents Antibiotics	– Gemcitabine, mitomycin C, platinums – VEGF and tyrosine kinase inhibitors – Bortezomib, carfilzomib – CsA, FK, everolimus, rapamycin – Adalimumab, imatinib – Ciprofloxacin, metronidazole, nitrofurantoin, trimethoprim/sulfamethoxazole
TMA associated with cancer: Cancer Chemotherapy Radiotherapy	– Especially solid organ neoplasms in metastatic phase (due to microvascular obstruction by tumor cells)
Methylmalonic aciduria	– It is a rare and heterogeneous congenital metabolic disorder of the metabolism of vitamin B12 or cobalamin. The consequence is an accumulation of methylmalonic acid and homocysteine in the blood and tissues, with an increase in the urinary excretion of both compounds – Confirmatory genetic testing should be performed in patients with positive metabolic screening
TMA associated with malignant hypertension	– Is a clinical term that defines the coexistence of hypertensive emergency and grade III–IV hypertensive retinopathy
TMA associated with DIC	– Patients are usually in septic shock – Prolonged prothrombin time and fibrinogen consumption

Table 102.4 Potential biomarkers of complement overactivation (17, 18)

Quantification of individual complement components and regulators		
Complement component	Function	Limitations
C3	Routine	Low in only 30% of aHUS
C4	Routine	Inherited deficiencies
FB	Alternative pathway	Other molecules
FI and FH	Often with low C3 levels	89% of aHUS—Normal FH levels
Properdin	Positive regulator	Specialized laboratories
MCP (CD46)	Flow cytometry	Low in 10% of aHUS
Measurement of complement activation markers		
Activation marker	Function	Limitations
C3a	Anaphylatoxin	Short decay time
C4d	Marker of CP	Elevated in SLE, RA
C5a	Elevated in aHUS	Short decay time Experimented laboratories
Ba, bb	Elevated in aHUS	Ba short decay time Elevated in STEC-HUS
C5b-9	Elevated in aHUS	Elevated in STEC-HUS and other kidney diseases
Functional analyses		
Assay	Function	Limitations
AP50	Alternative and terminal complement pathway	In aHUS acute phase, more serum is required to induce hemolysis due to consumption
Modified HAM test	Uncoated sheep erythrocytes	Discrepant results between laboratories
C5b-9 deposition on endothelial cells culture	Elevated in aHUS	Requires duplication and standardization

Therapy and Prevention

The gold standard treatment for aHUS patients is C5 blockade, if available. Eculizumab (short-acting) and Ravulizumab (long-acting) are the 2 complement blockers currently available in clinical practice. Both have shown in non-randomized prospective trials [19, 20] not only a high hematological response, but also an improvement in organ function (ESKD risk has decreased from 50–60% to ~10–15%), especially with its early introduction after the onset of the disease.

Acquired forms of aHUS (anti-FH antibodies) respond to C5 blockade but could be discontinued once the anti-factor H antibodies titer has been controlled. Despite the lack of a well-established treatment protocol for acquired forms, plasma exchange (PE) plus immunosuppression is the best option to maintain remission, or if C5 blockers are not available. In this disease, the aim is to achieve an 80% reduction in the antibody titers with PE (an average 5–7 sessions with fresh frozen plasma replacement) and different immunosuppression regimens (prednisone, cyclophosphamide, azathioprine, mycophenolate mofetil, and rituximab inhibit the formation of FH antibodies) [6].

In hereditary aHUS, the genetic variants detected could address the duration of treatment and the need for prophylactic C5 blockade in patients with ESRD due to aHUS who will receive a kidney transplantation.

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Part XIII

Hematologic Autoimmune Diseases

Autoimmune Hemolytic Anemia

103

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Abstract

Autoimmune hemolytic anemia (AIHA) is an acquired autoimmune disorder characterized by accelerated erythrocyte destruction due to autoantibodies against red blood cell surface antigens. The most important laboratory test for diagnosing AIHA is the **direct antiglobulin test (DAT)**, which detects antibodies or complement proteins on the surface of red blood cells. A positive DAT is strong evidence of AIHA in the setting of hemolytic anemia, but up to 10% of patients with AIHA may have a negative DAT. Once AIHA is diagnosed, it is essential to identify any underlying conditions that may be present in half of the patients, including other immune disorders, lymphoproliferative neoplasms, and infections. **Close collaboration between clinicians and laboratory professionals is essential to establish an accurate diagnosis of AIHA.**

Keywords

Autoimmune hemolytic anemia · Hemolysis · Direct antiglobulin test (DAT) · Elution test · Warm-autoimmune hemolytic anemia · Cold-agglutinin disease

Description of the Diseases

Autoimmune hemolytic anemia (AIHA) is a decompensated acquired hemolysis caused by the host's immune system acting against its red cell antigens [1]. The condition must meet two criteria: hemolysis causing anemia and the evidence of immune effectors acting against antigens on the red blood cell (RBC) surface. The hallmark of hemolysis is the accelerated destruction of RBCs, with the corresponding shortened lifespan. Usually, the diagnosis of AIHA is not challenging, and it can be established in the presence of hemolytic anemia with a positive direct antiglobulin test (DAT). However, neither hemolysis markers nor DAT alone can definitively define AIHA. The interpretation of the hemolytic markers may be challenging in the context of coexisting confounding conditions such as occult blood loss, vitamin and/or iron deficiency, renal or liver disease, and erythropoietin insufficiency [2]. On the other hand, a positive DAT can be found in healthy individuals without hemolysis, and conversely, 5–10% of patients eventually diagnosed with AIHA present with a negative DAT [3]. Therefore, the diagnostic process for AIHA requires a thorough integration of clinical and analytical data and close communication between the clinical and laboratory settings.

Classification of AIHA

Based on its pathophysiology, AIHA is typically classified into three groups: warm AIHA (wAIHA), accounting for 45–70% of cases; cold agglutinin syndrome (CAS) or diseases (CAD), comprising 15–25% of cases, and the paroxysmal cold hemoglobinuria (PCH).

wAIHA is mediated by polyclonal IgG autoantibodies (rarely, IgM) that react preferentially at 37 °C and recognize antigenic determinants located on the Rh protein or glycophorins. In less than half the cases, complement is activated to C3 on the RBC membrane, more frequently in association with LES. Antibody-coated RBCs are pitted or phagocyted by the spleen macrophages via the FcγRIII receptor. Pitted cells lose membrane, resulting in spherocytes that can be easily recognized on the blood smear and are trapped and destroyed into the splenic red pulp [4].

CAS is caused by polyclonal IgM autoantibodies directed against the I/i blood group system or, more rarely, the Pr antigens, and react preferentially at low temperatures. Sometimes, the IgM autoantibody is monoclonal, and the

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entity is named CAD. CAS follows acute infections, typically by *Mycoplasma pneumoniae*, and is transitory. On the contrary, CAD is a lymphoproliferative process recognized as a new condition in the last edition of the World Health Organization Classification of Hematolymphoid Tumors [5], and follows a chronic course, typically with winter exacerbations. These antibodies fix complement, which typically activates only up to C3, thus making red blood cells susceptible to extravascular phagocytosis by the mononuclear phagocytic system in the liver. In severe cases and acute exacerbations, intravascular hemolysis can occur due to complement activation up to the terminal attack complex [6, 7].

PCH is a very infrequent disease in adults, in whom it was associated with syphilis, but relatively frequent in children, in whom it can be seen after vaccinations and unspecific viral infections. PCH is mediated by a polyclonal IgG autoantibody (biphasic hemolysin) that reacts with the P antigen on the RBC membrane when blood flows through the small vessels of cold exposed acral zones. On returning to the general circulation, at 37 °C, the complement is activated up to the lytic complex, which results in intravascular hemolysis. The adult type of PCH presents with acute episodes of intravascular hemolysis after cold exposure and follows a chronic course. In contrast, the infantile form follows an acute course towards spontaneous resolution and does not require exposition to the cold.

Clinical Findings in AIHA

The cardinal manifestations of AIHA relate with both the anemic syndrome and hemolysis. Depending on the degree of anemia, patients may present with exertional dyspnea, fatigue, dizziness, cognitive impairment, and even fainting or chest pain. In a large series of primary AIHA patients, younger age, reticulocytopenia, Hb < 6 g/dL, or hemodynamic instability correlated with bad prognosis [8]. Signs linked to hemolysis include jaundice, enlarged spleen, and bilirubin gallstones in cases with a chronic course.

Acrocyanosis is a typical finding in CAS/CAD and may evolve to *livedo reticularis* in the more severe cases. In opposition to cryoglobulinemia, the Raynaud phenomenon and cutaneous ulcers are rare in CAS/CAD.

Clinical findings of potentially associated conditions, such as SLE, lymphoproliferative diseases, primary immunodeficiencies, or viral infections may or may not be evident at the time of diagnosis.

Laboratory Findings

Hemolysis Markers

The typical laboratory pattern in hemolytic anemia consists in a normocytic or slightly macrocytic anemia, increased unconjugated bilirubin and lactate dehydrogenase (LDH) levels, raised reticulocyte count in peripheral blood, and decreased haptoglobin levels. The blood smear shows polychromasia, and more specifically, spherocytes. Large RBC agglutinates are typical of CAS/CAD. In some cases of CAS/CAD the automated blood count may show spurious macrocytosis due to agglutination (great elevation of MCV and MCHC) with incongruities between hemoglobin and hematocrit values, artifacts that disappear on warming the blood sample to 37 °C.

None of these findings are completely sensitive or specific for the diagnosis of hemolytic anemia [2]. Despite its limitations, a haptoglobin limit of 25 mg/dL has high sensitivity (83%) and specificity (93%) for the diagnosis of hemolysis, being the most reliable serological marker for hemolysis [9]. Hemolysis markers are summarized in Table 103.1.

Table 103.1 Markers of hemolysis in AIHA

Hemolysis marker	Variation from normal	Comments
Hemoglobin	↓ to ↓↓↓	May be nearly normal if compensated by increased red cell production
Reticulocytes	↓ to ↑↑↑	↓ in 20–40% of the patients
LDH	↑ to ↑↑↑	Not specific: ↑ in high cellular turnover states Markedly ↑ in intravascular hemolysis
Haptoglobin	↓↓↓	May be ↑ in inflammatory states Not specific for hemolysis (↓ in hipo/ahaptoglobinemia, chronic liver diseases)
Bilirubin	↑	Disproportionately ↑ in Gilbert's syndrome May be normal in mild hemolysis
Peripheral blood smear	Spherocytes in wAIHA Agglutination in CAD/CAS	Spherocytes may be absent Essential to exclude other hemolytic conditions (schistocytes in TMA)
Hemosiderinuria/hemoglobinuria	–/+ in wAIHA/ CAD +/+++ in PCH	Marker for intravascular hemolysis

LDH lactate dehydrogenase, *wAIHA* warm AIHA, *CAD* cold agglutinin disease, *CAS* cold agglutinin syndrome, *TMA* thrombotic microangiopathy, *PCH* paroxysmal cold hemoglobinuria

Immunohematological Findings: The Direct Antiglobulin Test (DAT)

The DAT, or direct Coombs test (named after microbiologist Robin Coombs), aims to detect specific antibodies or complement molecules on the surface of RBCs by means of agglutination. Due to its small size, IgG antibodies and complement molecules cannot cause agglutination. To demonstrate their presence on the RBC surface, a commercial IgG antibody directed against the constant fraction of human IgG (antiglobulin) or the C3 fraction of complement must be added to play the role of a bridge between RBCs sensitized with IgG or C3, thereby causing an agglutinate that can be seen at the bare eye. The DAT is interpreted as negative (no agglutination) or positive for IgG and/or C3. The pattern of positivity is extremely important to guide further studies to reach a proper diagnosis and is shown in Table 103.2.

The indirect antiglobulin test (IAT) demonstrates the presence of free autoantibody in the patient's plasma. The positivity of the IAT has no prognostic significance but makes it difficult to find compatible blood for patients with wAIHA who require a blood transfusion.

AIHA with DAT Positivity for IgG (With or Without C3)

This is the typical pattern in the wAIHA. A positive DAT for IgG always requires confirmation by elution of the autoantibody from the RBC membrane, in order to exclude false-positive results due to unspecific deposition of IgG on the RBC surface, as it can occur in the hypergammaglobulinemia of liver cirrhosis, chronic inflammatory conditions or infectious diseases, or after some medications (e.g., ribavirine, cisplatinum, some cephalosporines). In these cases, elution will fail to show an autoantibody.

DAT positivity in the context of hemolysis can also occur in the immediate or delayed post-transfusion hemolytic reactions where DAT detects an alloantibody on transfused, incompatible RBC instead of an autoantibody. Elution will confirm the presence of an alloantibody, most frequently of the Kidd, Kell, and Rh systems.

In patients recently submitted to transplantation, either solid organ or hematopoietic cells, DAT positivity for IgG in the context of hemolysis should raise suspicion of the so-called "passenger lymphocyte syndrome" mediated by antibodies against the recipient RBC antigens produced by donor lymphocytes that "traveled" with the transplanted organ.

AIHA with DAT Positivity Only for Complement

The differential diagnosis includes CAS/CAD, and much less frequently, PCH and drug-induced AIHA. Laboratory etiological investigation of these anemias should include screening for cold agglutinins. If the screening is positive, antibody titration and thermal range should be examined because cold agglutinins at very low titers or limited thermal ranges are relatively frequent and lack any clinical relevance [6]. PCH is extremely rare in adults but it should be investigated in children with intravascular hemolysis by means of the Donath-Landsteiner test, which will show the presence of biphasic hemolysins.

AIHA with a Negative Direct Antiglobulin Test (DAT)

About 5–10% of patients with hemolytic anemia and a negative DAT are eventually diagnosed with AIHA, mostly of the warm antibody type. Both technical and immunological reasons may lay behind a negative DAT in wAIHA. Among technical issues, inadequate manipulation of the RBCs before performing the DAT, either because of insufficient or excessive washing, inappropriate temperature or pH may result in antibody elution from the RBC membrane or neutralization of the antiglobulin by traces of free IgG. Autoantibodies of predominantly IgG3 subclass are recognized very efficiently by the spleen macrophages, so that a few molecules on the RBC surface are enough to cause

Table 103.2 Immunohematological diagnosis of AIHA

Type	Antibody class	Target	Mechanism	Immunohematological findings
wAIHA	IgG (rarely IgM) -polyclonal	Public antigens on the Rh protein or glycophorins	Pitting/phagocytosis by spleen macrophages through FcγRIII	DAT: + IgG w/o C3 Eluate: IgG panagglutinin
CAS CAD	IgM – Polyclonal – Monoclonal	I/i system rarely: Pr, Sa, Sd	Pitting/phagocytosis by liver macrophages through C-receptor Complement-mediated i.v. hemolysis (rare)	DAT: +C3
PCH	IgG – polyclonal	P antigen	Complement-mediated i.v. hemolysis (rare)	DAT: +C3 Donath-Landsteiner test: + for biphasic hemolysins

AIHA autoimmune hemolytic anemia, *DAT* direct antiglobulin test, *wAIHA* warm AIHA, *CAS/CAD* cold agglutinin syndrome/disease, *PCH* paroxysmal cold hemoglobinuria severe anemia while undetected by the DAT. For several authors, low-affinity IgG antibodies and IgA and monomeric IgM autoantibodies would be behind some cases of DAT-negative wAIHA.

DAT-negative AIHA should be suspected when spherocytes are seen in the blood smear and other causes of hemolysis have been ruled out. Close communication with the immunohematology laboratory, repetition with close attention to technical details, search for antibodies in the eluate, and recurse to more sensitive (but less specific) tests is advisable. If DAT keeps being negative and the degree of suspicion is high, a short course of corticosteroid may be indicated [10].

Sensitivity, Specificity, and Predictive Value of the DAT

In many immunohematology labs, the DAT is performed manually and interpreted by the bare eye. Therefore, it requires trained technical personnel and close adhesion to well-designed procedures to avoid false results.

The DAT can be performed using three different physical supports: the traditional tube test, agglutination in columns of gel or micro-balls, and solid-phase on microtiter plates. The tube test has been reported to be the more specific (0.98) but least sensitive test (0.51), while tests using columns or microtiter plates seem to be more sensitive but less specific (0.83) [11, 12].

The positive predictive value of a DAT test for IgG is very high when complemented by the demonstration of panneglutinins in the eluate and a high clinical suspicion of wAIHA. On the contrary, the negative predictive value is not as high, as mentioned above.

Although several procedures have been described to increase the diagnostic performance of the DAT, none of them have been standardized for clinical practice [12].

Diagnostic Criteria for AIHA

There are no established diagnostic criteria for AIHA. Significant variability in the use of terminology to describe AIHA diagnosis has been found in the published studies so far. Of the 61 studies included in a recent systematic review [13], more than half defined AIHA as hemolytic anemia with positive DAT and exclusion of alternatives, while others used less complete definitions. In 2019, a group of experts published a consensus document with recommendations for diagnosis and treatment of AIHA [14]. The recommendations refer to both clinical and laboratory aspects of AIHA. All patients should have baseline hemolysis parameters and peripheral blood smear must be reviewed. DAT should be performed with monospecific antisera (anti-IgG; anti-C) that permit to distinguish laboratory patterns essential for an accurate diagnosis as previously exposed. They also prompt to recognize that about 5–10% of AIHA will be DAT negative, and make some additional recommendations to establish a proper diagnosis in this setting (including more sensitive techniques on even a corticosteroids trial). Diagnosis of CAD should include a DAT positive for C3, a cold agglutinin titer and bone marrow examination. CAD should be differentiated from secondary CAS. Once the diagnosis is reached, evaluation for underlying disorders is mandatory. wAIHA patients should be evaluated for autoimmune diseases, lymphoproliferative disorders or immune deficiency disorders. Patients with CAD should be evaluated for clonal B-cell disorder. The document also prompts to suspect more infrequent types of AIHA in the appropriate clinical setting, such as mixed AIHA in patients with DAT positive for IgG and C3 and presence of symptoms of CAD, or PCH in a patient with fitting history.

Table 103.3 summarizes the proposed investigations to rule out the most common AIHA-associated conditions.

Table 103.3 Recommendations for the diagnosis of secondary AIHA

Disease or condition	In all patients	Only in some circumstances
SLE or other autoimmune diseases	ANA Anti-dsDNA and other specificities if ANA>1/80	APA CH50, C3, C4 in case of SLE
Lymphoproliferative diseases	Serum protein electrophoresis Immunoelectrophoresis Peripheral blood B-lymphocyte immunophenotype CT scan (unless obvious SLE)	Bone marrow biopsy if monoclonal gammopathy or hypogammaglobulinemia, lymph nodes, and/or disproportionate splenomegaly on the CT scan and/or atypical lymphocyte population Lymph node biopsy
Primary immunodeficiencies	IgG, IgA, and IgM levels	Extended phenotype of T/NK and memory B cells Post vaccine serology (tetanus toxoid, pneumococcus)
Infections	HIV and HCV test HBV test (pre-therapeutic)	CMV, EBV, parvovirus B19 Mycoplasma in CAS

SLE systemic lupus erythematous, *ANA* anti-nuclear antibodies, *ds-DNA* double stranded DNA, *CT* computed tomography, *APA* antiphospholipid antibodies, *HIV* human immunodeficiency virus, *HCV* hepatitis C virus, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus

Current and Emerging Therapeutic Strategies for AIHA

An accurate diagnosis of AIHA is important for designing an appropriate treatment plan. General measures for all patients include treatment of any identified underlying cause requiring treatment, acid folic supplementation to attend the demands of an increased erythropoiesis in response to hemolysis, extended compatibility testing in case of the need for red cell transfusion, and venous thromboembolism prophylaxis during acute exacerbations of the disease. In wAIHA, corticosteroids remain the mainstay of first-line treatment. However, in 20 to 30% of cases refractoriness is observed. In most current treatment consensus, the anti-CD20 monoclonal antibody rituximab has displaced splenectomy as the second-line treatment due to a lower rate of associated adverse effects, even though splenectomy was considered a second-line treatment for many years. Other options include immunosuppressants and even chemotherapeutic agents as vincristine [15].

In CAD, it is recommended not to initiate treatment unless there is symptomatic anemia with hemoglobin below 100 g/L. Since many patients have mild or moderate forms of the disease, they can be managed with cold protection measures. Even in the case of acute exacerbations, if there is a clear trigger, a conservative approach could be considered, with transfusion support and treatment of the underlying cause. When treatment is indicated, it is directed at the pathogenic B-cell clone, with rituximab as the first line, with or without bendamustine [6].

The expansion of the therapeutic arsenal in recent years in the field of hematology has increased the treatment possibilities for relapsed or refractory AIHA. New drugs targeting B lymphocytes (ibrutinib), T lymphocytes (alemtuzumab, MMF), plasma cells (bortezomib, daratumumab), complement (sutimlimab, pegcetacoplan, eculizumab), or IgG-driven hemolysis (fostamatinib) have not been developed specifically for AIHA treatment, but many of them have therapeutic targets involved in its pathophysiology and are being explored in the context of clinical trials [16, 17].

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104

Pernicious Anemia

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Abstract

Pernicious anemia (PA) is the most common cause of vitamin B12 deficiency worldwide. PA is an autoimmune disease characterized by the production of autoantibodies directed to the intrinsic factor (IF) and the parietal cells (PC) of the gastric mucosa. Pathophysiology mechanisms are still unclear, but there is evidence that supports the presence of immunoglobulins A, G, and M, as well as autoreactive T lymphocytes into gastric mucosa, blocking binding sites of cyanocobalamin and decreasing its absorption, with consequent peptic cell destruction and loss of IF. Diagnosis can be challenging because of clinical manifestations, differential diagnosis, blood test availability, serum cobalamin assay results, and titers of IF and PC antibodies. The onset of PA is progressive and insidious; the clinical features are nonspecific and are developed over 20 to 30 years. Different kinds of cyanocobalamin supplementation are now available for the management of the disease.

Keywords

Pernicious anemia · Vitamin B_{12} deficiency · Intrinsic factor · Parietal cells

Introduction

Pernicious anemia (PA) is defined by vitamin B12 deficiency and positive gastric parietal cell or intrinsic factor antibodies (PCA/IFA) [1]. It is an autoimmune disease characterized by chronic atrophic gastritis (CAG) and cyanocobalamin deficiency (CD), resulting in megaloblastic anemia because of an impaired absorption of cobalamin. PA is the most common cause of CD worldwide. Two types of autoantibodies have been identified: (a) Immunoglobulin G directed against Intrinsic Factor (IF), and (b) Immunoglobulins A, G, and M, directed against parietal cells (PC). Due to the absorption decrease and consequent lack of cyanocobalamin, there is impaired DNA synthesis and megaloblastic anemia development [2, 3].

Macrocytic cells and their precursors are prone to suffer hemolysis and apoptosis in bone marrow related to inefficient erythropoiesis. These derangements can be found in blood tests as increased levels of lactate dehydrogenase (LDH) and indirect bilirubin; also, a decreased level of haptoglobin can be shown. Primary hemolytic anemia (PHA) can be suspected by some practitioners instead of megaloblastic anemia due to PA [4].

Nowadays, PA is considered as another risk factor for gastric carcinoma [1] and is linked to other autoimmune disorders, such as Hashimoto thyroiditis, diabetes type 1, and pure red cell aplasia [2]. Diagnosis is usually challenging; CD and macrocytic anemia can depend on various clinical entities.

Epidemiology

PA is more prevalent among those aged 60 years and older, particularly those of Northern European ancestry. The prevalence is hugely affected by age, ranging from 0.1% in the general population to 1.9% in older adults above the age of 60 years. PA accounts for 20%–50% of the etiology of CD in

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adults. Although the incidence of PA rises with age, it varies geographically.

There is evidence that PA affects all racial and ethnic groupings. For instance, in Chinese individuals with megaloblastic anemia Wun Chan et al. discovered that 76% of 296 individuals had PA [5]. PA can occur in minors under the age of ten (juvenile pernicious anemia), although it is typically diagnosed in women around the age of 35.

History

In 1855, Thomas Addison described his classic definition of PA. Austin Flint linked histological changes in the stomach to PA. Anton Bierner first named “Pernicious Anemia” this disease in 1872. In 1926, George R. Minot and William P. Murphy detailed their liver feeding and subsequent refinements; their research led to the cure for PA and won them the Nobel Prize in 1934. The anemia was thought to be caused by a lack of extrinsic factor (food containing cobalamin), blood antibodies against fetal cells, and an inhibitor of IF. This entity was highly associated with underlying autoimmune CAG and the discovery of PCA and IFA demonstrated part of the pathogenesis [6].

Pathogenesis

Normally, cobalamin needs three main components to be absorbed: IF, transcobalamin and haptocorrin. Once digested by saliva, the haptocorrin-cobalamin complex is subjected to proteolytic activity by pepsin and releases around 70% of cobalamin. In the stomach, IF binds to cobalamin and carries it to the ileum, where it is absorbed by endocytosis. In serum, this substance has two forms: holotranscobalamin and holohaptocorrin, which are metabolized and stored in the liver.

The CD is the hematologic manifestation of CAG, which affects the fundus and the body of the stomach. PA is characterized by the production of PCA and IFA with a consequent absence of cobalamin absorption. The etiology of PA is unclear; it is known that prolonged activity of gastric dendritic cells conduces signals for CD4$^+$ T lymphocytes in paragastric lymphoid tissue. These T lymphocytes stimulate B lymphocytes to produce PCA and IFA.

The autoimmune response consists of PCA and IFA (Immunoglobulin A, G and M isotypes) against α and β subunits of the H$^+$/K$^+$/ATPase pump (proton pump). The antibodies lead to the destruction of GPC, resulting in CAG [2, 6, 7].

The PA-related CD that manifests clinically is a lengthy process that may lead to potentially irreversible hematological and neurological complications. Gastric atrophy is the end stage of asymptomatic autoimmune gastritis that precedes the atrophy by 10–20 years. While PCA can activate the complement system and induce the destruction of parietal cells in laboratory conditions, it is improbable that these autoantibodies have a harmful effect in living organisms due to the inaccessibility of stomach H+/K + -ATPase to antibodies circulating in the bloodstream. This finding could reflect cell loss due to antibody-triggered apoptosis, as has been described in other pathophysiological mechanisms. In this context, pathogenic CD4 T cells are reactive to the parietal cell autoantigen, H$^+$/K$^+$ ATPase, and are controlled by CD4-CD25 T cells in an immunosuppressive cytokine-independent manner. Current results suggest that the presence of IL-10 and TGF-b may be necessary due to the intricate characteristics of T cells involved in the development of the disease, as well as the role played by induced regulatory T-cell populations.

The concentration of IFA and PCA in relatives suggests a genetic predisposition to PA and the association between disease and the onset of endocrinopathies.

Clinical Manifestations

PA is a slow-developing disease; after five years of evolution, the first clinical manifestation of vitamin B12 deficiency appears. The main symptom is megaloblastic anemia, but sometimes, neurologic manifestations could present earlier. Despite PA being a rare disease, secondary vitamin B deficiency causes, such as a vegan diet, a history of ileal disease or resection, and total or partial gastrectomy, must be excluded.

The onset of PA is gradual and insidious, and the classic triad (weakness, aching tongue, and paresthesia) is not the most prominent clinical manifestation. Symptoms of anemia are the typical presentation, but most cases are identified through routine hematologic testing. Table 104.1 lists the main clinical characteristics of PA.

Table 104.1 Common clinical features of pernicious anemia

Clinical manifestations	
Neurological	Confusion, headache, difficulty to focus, memory loss, imbalance cognitive decline, paresthesia, numbness, cerebellar and cerebral degeneration, peripheral neuropathy
Psychiatric	Depression, personality changes, psychosis, catatonia, emotional lability, dementia, intellectual deficit, hallucinations, irritability
Otolaryngologic	Glossitis, hypogeusia/ageusia, oral ulcers, burning mouth syndrome
Cardiopulmonary system	Dyspnea, palpitations
Gastrointestinal system	Diarrhea, dyspepsia, decreased appetite, hepatosplenomegaly
Constitutional	Tiredness, lethargy, anorexia, weight loss.
Cutaneous	Hyperpigmentation, erythema nodosum

Axonal degeneration and neuronal death caused by a vitamin B12 shortage are linked to neurological problems such as neuropathy and lesions in the posterior and lateral columns of the spinal cord and brain [8]. Peripheral neuropathy is the earlier neurologic manifestation and is usually symmetric predominantly in the legs. The physical exploration in these patients shows a decrease of sensitivity of vibration, a test of sharpness or dullness, and light touch, when the alteration is severe, could show a positive Romberg test. Some patients could show subacute combined degeneration with limb weakness, ataxia, or sometimes visual disturbance. The median duration of symptoms at diagnosis was six weeks (range 2–24 weeks) in those who had complete recovery and 12 weeks (range 1–84) in patients with partial recovery.

Although relatively infrequent pallor, dry skin, jaundice, tender, smooth, and red tongue (glossitis). A psychiatric evaluation is recommended for all patients with severe illness.

Hematologic Features

Serum biomarker tests should screen for PCA to gastric H/K ATPase and IFA. Screening tests using a combination of pepsinogen 1 (P1), pepsinogen 2, pepsinogen 1/pepsinogen 2 ratio, and gastrin-17 reliably identify the presence of chronic atrophic gastritis. Loss of zymogenic cells leads to low pepsinogen levels, while loss of acid secretion leads to hypergastrinemia. These serum biomarker tests have been coined the “serological gastric biopsy”. Serum ghrelin, a molecule mainly produced by endocrine cells of the gastric oxyntic mucosa, is an emergent and promising new test for gastric atrophy. Serum ghrelin was reported to be associated with the highest sensitivity and specificity (97.3 and 100%, respectively) in detecting gastric atrophy and was superior to pepsinogen I/II ratio and gastrin [9].

The most crucial laboratory finding observed in PA is variable immunodeficiency and low serum immunoglobulin concentrations. Low serum immunoglobulin levels and variable immunodeficiency have been detected in the laboratory. Several autoimmune diseases are interconnected, including autoimmune thyroiditis, autoimmune diabetes, Addison’s disease, primary ovarian failure, Graves’ disease, vitiligo, myasthenia gravis, Lambert-Eaton syndrome, and diabetes mellitus type 1 [10, 11].

Pathological Features

Two varieties of atrophic gastritis exist: A, associated with PA, with PCA and IFA, and achlorhydria, whereas B, associated with *Helicobacter pylori* infection.

The most common lesions in gastric-biopsy specimens from PA patients are mononuclear cellular infiltrates in the submucosa extending into the lamina propria between the gastric glands; degenerative changes in parietal cells and zymogenic cells accompany the extension of the cellular infiltrate into the mucosa. The cellular infiltrate includes plasma cells and T cells [12]. After that, the mucosa becomes atrophic, containing a few pepsin-secreting and parietal cells, and intestinal metaplasia is established. Chronic atrophic gastritis in PA is also associated with an increased risk of intestinal-type gastric cancer and gastric carcinoid tumors. The latter is presumably due to prolonged achlorhydria resulting from parietal-cell loss, compensatory hypergastrinemia, and argyrophilic cell hyperplasia.

In the bone marrow biopsy and aspirate the erythroid precursors are large and oval, the nucleus is large and contains course motley chromatin clumps, having a checkerboard appearance. Nucleoli are visible in the more immature erythroid precursors. Giant metamyelocytes and bands are present, and the mature neutrophils and eosinophils are hypersegmented [13]. The bone marrow histology is similar to erythrocytic macrocytosis; when the mean cell volume (MCV) is greater than 100 fL, the MCV and mean corpuscular hemoglobin (MCH) increase, with a mean corpuscular hemoglobin concentration (MCHC) within the reference range. An MCV above 120 fL. is associated with PA in more than 95% of cases. In addition, the peripheral blood may show mild leukopenia and thrombocytopenia or pancytopenia, which parallel the severity of the anemia because vitamin B12 deficiency affects all hematopoietic cell lineages. Examination of the marrow is not indicated if the diagnosis is unequivocal; the earliest sign of megaloblastosis reflected in the peripheral blood smear is hypersegmentation of the polymorphonuclear leukocytes followed by the appearance of oval macrocytes and anisopoikilocytosis [14].

Serological and Biochemical Features

Request a complete blood count and a blood test. Elevated red blood cells mean corpuscular volume (macrocytosis) and hypersegmented neutrophils point toward cobalamin deficiency. About a third of patients with B12 deficiency may not have macrocytosis. Macrocytosis can also occur with folate deficiency, liver disease, and alcoholism. Lactic dehydrogenase (LDH) levels are characteristically very increased. Diagnosis of PA is supported by measuring blood levels of cobalamin and folate; cobalamin is low in most patients with cobalamin deficiency. Patients with vitamin B12 deficiency will have serum levels <170 pg/mL, with symptomatic patients usually having levels <100 pg/mL.

There are two sensitive metabolic markers to support the diagnosis: plasma methylmalonic acid (MMA) and plasma total homocysteine (tHC), although their concentrations do not predict clinical manifestations. They are elevated in vitamin B12 deficiency, and they rule out cobalamin deficiency when they are normal [15].

There is no "gold standard" test for PA, and there is a lack of quality evidence regarding the diagnostic accuracy of tests [15]. IFA are highly specific (95–100%) for PA, although only 60% of PA patients will have positive titers. A negative result does not exclude the disease due to the low sensitivity of the test (50–60%) [10].

A Schilling test will confirm that vitamin B12 deficiency results from intestinal malabsorption due to IF deficiency. The Shilling test assay for cobalamin absorption measures urinary radioactivity after giving an oral dose of radioactive cobalamin. Absorption is low in PA and increases if radioactive vitamin B12 is administrated along with IF [8], but some authors conclude that this test is obsolete.

Some patients with autoimmune thyroiditis can also have PCA, whereas PA patients have antibodies against thyroid epithelium, lymphocytes, and renal collecting duct cells.

The diagnosis is virtually certain in the presence of megaloblastic anemia. A positive test for anti-IFA or PCA (by immunoblotting, ELISA, and chemiluminescent immunoassay methods) identifies an autoimmune basis for gastric atrophy in PA. PCA are found in 90% of patients with PA but have low specificity and are seen in atrophic gastritis without megaloblastic anemia and in other autoimmune disorders [16].

Diagnostic Criteria

A definitive diagnosis of PA could be difficult because the Schilling test is becoming outdated and lacks a validated B12 absorption test. However, diagnosing PA depends on the presentation of megaloblastic anemia, low concentration of serum vitamin B12, gastric atrophy, and antibodies to GPC or IF. Typically, the anemia is macrocytic and normochromic, with diminished absolute reticulocyte counts. In addition, red blood cells show notable anisopoikilocytosis and several oval macrocytes. Finally, it is important to consider that macrocytosis might be absent in nearly 30% of PA patients when iron deficiency is associated. Schistocytes may be seen in megaloblastic anemias due to erythroblast cytoskeletal fragility, demonstrating the extremity of dyserythropoiesis [8].

Histological assessment after a bone marrow biopsy and aspiration are frequently unnecessary. Some findings are hypercellularity with a shift toward immaturity [14].

Chronic atrophic gastritis can be detected based on high fasting serum gastrin levels and low levels of serum pepsinogen I. In some cases, endoscopy might be helpful in ruling out gastric carcinoid and other GC [17].

Prognosis

Decades ago, before efficient management existed, PA could be fatal. Since then, the prognosis has been spectacular with a pertinent treatment, except for patients with subacute combined system degeneration. The B12 supplementation ceases the progression of neurological complications only in a few patients. Moreover, poor prognosis is present when gastric cancer or carcinoid tumors are diagnosed in late stage. Therefore, regular endoscopies, including those without symptoms, are recommended every 5 years [18]. Some psychiatric manifestations like emotional lability and psychosis may improve quickly.

Predicting the Role of Autoantibodies

Serum GAC might predict auto-immune gastritis. PCA and IFA are uncommonly assessed in patients with megaloblastic anemia. IFA are highly specific for PA (with a limited sensitivity), and their occurrence with megaloblastic anemia increases the possibility of a PA diagnosis [8].

Other causes of macrocytic anemia and cobalamin deficiency are listed in Table 104.2.

Table 104.2 Causes of macrocytic anemia and cobalamin deficiency

Causes of macrocytic anemia	Causes of cobalamin deficiency
Hypoplastic anemia, Myelodysplastic syndrome Folate deficiency Liver disease (alcoholic, advance cirrhosis, poor dietary intake) Hemolytic anemia Response to hemorrhage Drugs (e.g., methotrexate, azathioprine, acyclovir, phenobarbital)	Total or partial gastrectomy Gastric bypass Corpus-predominant *Helicobacter pylori* gastritis Inflammatory bowel disease Mild atrophic gastritis Use of metformin or drugs that block stomach acid Vegan of vegetarian diet, or diet low in meat and dairy products

Table 104.3 Pharmacological treatment of pernicious anemia

Acute treatment	Dose	Duration	Maintenance	Dose	Duration
OH Cbl	100 µg IV every other day	3 weeks	OH Cbl	100 µg IV	Every 3 months for life
OH Cbl	100 µg IV 3 times a week	2 weeks 120 days	OH Cbl	100 µg IV	Once every 3 months for life
OH Cbl	1000–2000 mg VO daily		Not available data		
OH Cbl	1000 mg VO		Not available data		

OH Cbl Hydroxocobalamin

Therapeutic Management

In 2019, the British Society of Gastroenterology guidelines suggested that a baseline endoscopy with biopsies should be regarded in subjects 50 years or older, with laboratory tests suggesting PA, determined by B12 vitamin deficiency and either positive gastric parietal cell or IFA [1].

Long-term therapy with an intramuscular (IM) injection of 1000 µg of B12 cyanocobalamin administered daily for 1 to 2 weeks, followed by injections for 1 to 2 months every week, afterward infection every month, or every 2 to 3 months [19]. For maintenance, patients can continue IM injections, or patients may have high-dose oral B12 supplementation. If the vitamin B12 stores last for 5 years, intramuscular shots every year are more than enough to maintain a good response. Sublingual and intranasal formulations are available; however, they are not widely recommended [20].

The management should be monitored by reticulocyte counts, LDH, and an appropriate rise in hemoglobin (Hb) levels. LDH levels decrease, and Hb levels increase by about 1 g/dL/wk. A rise in LDH might denote a relapse [19]. In patients with PA, blood transfusions are seldom needed.

Therapeutic management is summarized in Table 104.3.

Vitamin B12 must be replaced with folic acid and oral iron must be administered because iron stores may deplete.

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Idiopathic Aplastic Anemia

105

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Abstract

Aplastic anemia is a rare disease characterized by presenting bone marrow failure and pancytopenia, with no trace of myeloproliferative or fibrotic processes. It confers a significant risk for morbidity and death due to its progressive natural history and complications related to suboptimal therapy. The pathophysiology is immune-mediated in most cases, with activated type 1 cytotoxic T cells implicated. The molecular basis of the aberrant immune response and deficiencies in hematopoietic cells is now being defined genetically; examples are telomere repair gene mutations in the target cells and dysregulated T-cell activation pathways. Establishing an accurate etiology of aplastic anemia is challenging but also critical to appropriate management, especially differentiating between acquired and inherited forms of the disease. Aplastic anemia can be cured or alleviated by stem-cell transplantation or immunosuppressive drug therapy. Immunosuppression with antithymocyte globulins (ATGs) and cyclosporine effectively restores blood-cell production in most patients, but relapse and especially the evolution of clonal hematologic diseases remain problematic. Allogeneic stem-cell transplant from histocompatible sibling donors is curative in the great majority of young patients with severe aplastic anemia; the major challenge is extending the benefits of transplantation to patients who are older or who lack family donors.

Keywords

Aplastic anemia · Pancytopenia · Stem-cell transplantation

Definition

The term "aplastic anemia" was introduced by Vaquez and Aubertin in 1904. The word "aplastic" is derived from the Greek "a" and "plasso" meaning "without form." "Anemia" has resulted in confusing terminology; it derives from the early ability to measure red cells in a hematocrit. Most patients with aplastic anemia (AA) have pancytopenia, with decreased platelets, white cells, and erythrocytes. Combining peripheral cytopenias with decreased or absent bone marrow precursor cells characterizes aplastic anemia. Yet a seemingly "empty" bone marrow may be entirely capable of supporting normal hematopoiesis. Conversely, bone marrow failure can occur without low cellularity, as in the myelodysplastic syndromes and paroxysmal nocturnal hemoglobinuria. Although there are many known etiologies (Table 105.1), the cause of AA is generally difficult to determine in an individual patient, and most cases, no causal etiology can be found.

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Table 105.1 Classification of aplastic anemia

Acquired aplastic anemia
Secondary aplastic anemia Irradiation
Drugs and chemicals
Regular effects
Cytotoxic agents
Benzene
Idiosyncratic reactions
Chloramphenicol
Nonsteroidal anti-inflammatory drugs
Antiepileptics
Gold
Other drugs and chemicals
Viruses
Epstein–Barr virus (infectious mononucleosis)
Hepatitis virus (non-A, non-B, non-C, non-G hepatitis)
Parvovirus (transient aplastic crisis, some pure red cell aplasia)
Human immunodeficiency virus (acquired immunodeficiency syndrome) immune diseases
Eosinophilic fasciitis
Hypoimmunoglobulinemia
Thymoma and thymic carcinoma
Graft-versus-host disease in immunodeficiency
Paroxysmal nocturnal hemoglobinuria
Pregnancy
Idiopathic aplastic anemia
Inherited aplastic anemia
Fanconi's anemia
Dyskeratosis congenita
Schwachman–Diamond syndrome
Reticular dysgenesis
Amegakaryocytic thrombocytopenia
Familial aplastic anemias
Preleukemia (e.g., monosomy 7)
Nonhematologic syndromes (e.g., Down, Dubowitz, Seckel)

Epidemiology

The incidence of AA is 0.6 to 6.1 cases per million population; this rate is primarily based on data from retrospective reviews of death registries [1]. The male-to-female ratio is approximately 1:1. Although it occurs in all age groups, a first peak in the incidence is observed in childhood, and a second is found in the 20- to 25-year-old age group. Though considered to be rare in the United States and Europe (2–3 million), its incidence is relatively high elsewhere, particularly in Asia [2]. This geographic variation likely stems from environmental rather than genetic risk factors because the Japanese population in Hawaii manifests rates of AA similar to those of other Americans [3]. Studies have not been able to attribute the increased risk of AA in the Far East to specific agents, such as chloramphenicol, widely used in Asia [4].

Pathophysiology

Immune AA lies on a spectrum of bone marrow and blood cell diseases. Three interrelated explanations exist for AA [5].

- Direct damage: It can be iatrogenic or dose-dependent, resulting from chemotherapy and radiotherapy; medications can also cause it. It manifests itself with a notable reduction in hematopoiesis [6].
- Immune damage: Several studies have shown that immunological disorder originating in T lymphocytes, mediated by hematopoietic stem cells, is the main factor involved in the pathogenesis of AA. Additionally, many proinflammatory cytokines have been associated, including interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), among others are involved [7, 8].
- Syndromes causing bone marrow failure, whether congenital or acquired. In most cases, the problem is the presence of defective DNA due to mutations, which generate apoptosis and degeneration of hematopoietic stem cells, which progresses to severe AA. On the other hand, clonal diseases also occur, leading to pathologies such as myelodysplasia and paroxysmal nocturnal hemoglobinuria [9].

One peculiar feature of white blood cells in AA is the length of the telomeres. Telomeres are short in one-third to one-half of patients [9]. The first hypothesis that blamed telomere shortening on stem-cell exhaustion was dismissed by discovering gene mutations that repair and protect telomeres. The working premise these days is that those mutations are genetic risk factors in acquired AA, probably because they confer a quantitatively reduced hematopoietic stem-cell compartment that may also be qualitatively inadequate to sustain immune-mediated damage.

Finally, there is no satisfying mechanism to explain clonal escape evolving to other hematologic diseases characterized by the proliferation of distinctive cell clones.

Clinical Manifestations

Symptoms related are anemia, progressive weakness, pallor, and dyspnea; neutropenia, frequent and persistent minor infections, or sudden onset febrile illness; thrombocytopenia, ecchymoses, mucosal bleeding, and petechiae may be detected [10]. Major bleeding from any organ can occur in AA but is usually not seen until late in the course of the disease and is generally associated with infections or traumatic therapeutic procedures (e.g., intravenous line placements). Laboratory tests will demonstrate macrocytic normochromic anemia with neutropenia and thrombocytopenia [11]. The infections in AA patients are typically bacterial, including sepsis, pneumonia, and urinary tract infections. However, invasive fungal infection is a common cause of death, especially in subjects with prolonged and severe neutropenia. The physical examination is generally unremarkable except for bruising and petechiae, as noted above. Hepatosplenomegaly and lymphadenopathy are usually absent.

Diagnosis

Establishing a diagnosis of AA can be challenging, but it is critical to appropriate management, significantly differentiating between acquired and inherited forms of the disease [11]. Signs and symptoms at the presentation are illustrated in Table 105.2.

The complete blood count suggests the possible presence of aplastic anemia, which reveals pancytopenia and absolute reticulocytopenia, suggesting bone marrow failure. The red blood cells are usually normocytic but occasionally may be macrocytic. Examination of the peripheral blood smear shows that the remaining elements, while reduced, are morphologically normal.

The diagnostic criteria for AA are as follows: the presence of bone marrow hypocellularity and two or more cytopenias (reticulocytes less than 1% or less than 40,000/μL, neutropenia less than 500/μL, or thrombocytopenia less than 20,000/μL). The non-severe disease has less than 30% bone marrow cellularity; the severe disease has less than 25% cellularity or less than 50% cellularity containing fewer than 30% hematopoietic cells, and very severe disease is the severe criteria plus neutropenia less than 200/μL. The aspirate of bone marrow has little yield ("dry tap") [11, 12]. Also, bone marrow biopsy is essential: it will be markedly hypocellular and devoid of marrow progenitors. Table 105.3 illustrates the criteria for AA.

Genetic testing with flow cytometry and fluorescence in situ hybridization (FISH) is helpful to exclude hematologic malignancies responsible for pancytopenia. Additional testing depends on the underlying condition responsible for bone marrow failure.

Table 105.2 Presenting symptoms of aplastic anemia

Symptoms	Number of patients
Bleeding	41
Anemia	27
Bleeding and anemia	14
Bleeding and infection	6
Infection	5
Routine examination	8
Total	101

Adapted from Williams DM, Lynch RE, Cartwright GE. Drug-induced aplastic anemia. Semin Hematol 1973; 10: 195

Table 105.3 Definition of aplastic anemia with severity criteria

Non-severe	Hypocellular BM*, less than 30% bone marrow cellularity, with peripheral blood values not meeting criteria for severe aplastic anemia
Severe	BM cellularity <25% (or <50% if <30% of BM is hematopoietic cells) AND = 2 of the following: • Peripheral blood neutrophil count <0.5 × 10%/L • Peripheral blood platelet count <20 × 10%/L • Peripheral blood reticulocyte count <20 × 10^9/L
Very severe	As mentioned above, but peripheral blood neutrophil count must be <0.2 × 10^9/L

BM bone marrow

Treatment

Supportive Care The initial management in most AA patients consists of blood transfusions, platelet concentrates, and infection prophylaxis/treatment.

- Blood Transfusions: Patients with severe AA may require leukoreduced red blood cells for hemoglobin less than 7 mg/dL to maintain adequate levels of red blood cells.
- Platelet Transfusions: Patients with platelets less than 10,000/μL or less than 50,000/microliters for active blood loss.

Immunosuppressive Therapy Older patients (50 years or older) in good health and young patients without a hematopoietic stem cell transplant donor receive full-dose immunosuppressive therapy using eltrombopag, horse/rabbit antithymocyte globulin (ATG), cyclosporine A, and prednisone [13].

As defined above, definitive therapies are immunosuppression or stem-cell transplantation for severe AA. The most acceptable immunosuppression regimen is an antithymocyte globulin (ATG) combined with cyclosporine [14]. This therapy aims to suppress the immune system, allowing the bone marrow to recover.

- ATG eliminates antigen-reactive T lymphocytes and induces hematologic responses in aplastic anemia.
- Cyclosporine A inhibits the production and release of interleukin-2 (IL-2) and inhibits IL-2-induced activation of resting T-lymphocytes. Although severe AA can respond to cyclosporine alone, it is less effective than ATG alone or ATG plus cyclosporine.
- Prednisone induces cell death of immature lymphocytes.

About 60% of patients are responders at 3 or 6 months after initiation of ATG treatment [15]. Responders have much better survival prospects than non-responders, and the outcomes are related to patient age: 5-year survival of >90% of children compared with about 50% survival for adults older than 60 years in the collective European experience [16].

Relapses occur in 30–40% of patients, defined as a requirement for additional immunosuppression. The reinstitution of cyclosporine usually reverses declining blood counts, and when required, a second round of ATG is adequate. As much as it is known today, relapse does not confer a poor prognosis [17].

Hematopoietic Stem Cell Transplant (HSCT) Replacement of a failed bone marrow is curative of the underlying disease. For younger patients with a matched donor, hematopoietic stem cell transplantation (also known as a bone marrow transplant) may be considered. This procedure involves replacing the diseased bone marrow with healthy stem cells from a donor. An allogeneic transplant from a matched sibling donor cures most patients with high 5-year survival rates [18]. Graft-versus-host disease (GVHD) remains a severe problem for older patients (40–45% > 20 years of age), even with routine cyclosporine prophylaxis. Chronic GVHD raises the risk of death and often requires years of immunosuppressive therapy [19].

Androgens Some patients progress to severe disease, whereas others remain stable and may not require intervention. The two most acceptable modes of treatment options are immunosuppressive and androgen therapies. Danazol, a synthetic androgen, may be prescribed in some cases. It stimulates the production of red blood cells and platelets in the bone marrow (20).

Regular follow-up appointments and monitoring are essential to assess the response to treatment and manage potential complications. It is important to note that aplastic anemia can be a chronic condition, and long-term management may be necessary. Each case is unique, and treatment plans should be tailored to the individual needs.

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106

Acquired Adult Pure Red Cell Aplasia

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Abstract

Pure red cell aplasia (PRCA) is a rare hematological disorder characterized by severe anemia due to a selective failure of erythropoiesis. PRCA exhibits diverse epidemiological patterns worldwide. PRCA is classified into congenital, primary, and secondary forms. Congenital PRCA, such as Diamond-Blackfan anemia, involves genetic abnormalities, whereas transient erythroblastopenia of childhood lacks a clear etiology. Acquired PRCA in adults can result from various factors, including drugs, infections, autoimmune diseases, malignancies, and pregnancy. The pathophysiology of PRCA varies; parvovirus B19 directly damages erythroid precursors, while other cases involve immunologically mediated mechanisms, including antibody-mediated and T-cell-mediated processes. Clinical manifestations often appear in advanced stages, with symptoms of anemia. Laboratory findings show severe reticulocytopenia, normocytic normochromic anemia, and diminished erythroblasts in the bone marrow. Treatment strategies involve addressing the underlying cause, discontinuing offending medications, and thymectomy for thymoma cases. Immunosuppressive therapy with cyclosporine is the first-line treatment. Other therapies may be considered for refractory cases, including cyclophosphamide, azathioprine, IV immunoglobulin, plasmapheresis, rituximab, and alemtuzumab. Spontaneous remission occurs in a minority of patients, while most respond to immunosuppressive therapy. The prognosis varies based on the type of PRCA and underlying conditions.

Keywords

Pure red cell aplasia · Anemia · Reticulocytopenia · Erythroblasts · Large granular lymphocytes · Erythropoietin

Pure red cell aplasia (PRCA) is characterized by anemia with severe reticulocytopenia caused by selective failure of erythropoiesis. Kaznelson first described this disease in 1922. PRCA is a rare disorder; it affects all age groups worldwide without known ethnic or racial predisposition [1]. Nakazawa et al. [2] recently published a nationwide study in Japan. They found an incidence of 1.06 per million with a female-to-male ratio of 1.5:1 with a median age of 73 years (18–99 years). The etiology in 69% of the 1055 cases was idiopathic. This study contrasts with Thibile et al. [3], who also found a preponderance of females; nevertheless, the median age was 35 years (range 20–62), and all patients were HIV positive. These studies highlight the different epidemiology around the world depending on several factors.

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Classification of PRCA

Typically, PRCA is classified into three different forms: congenital, primary, and secondary [4]. The congenital form of PRCA, Diamond-Blackfan anemia, is a genetic disease with chromosomal and physical abnormalities [5]. Transient erythroblastopenia of childhood is a heterogeneous disease with unclear etiology [6].

The causes of acquired PRCA in adults include a primary disorder (isolated PRCA) or secondary PRCA (Table 106.1). The most common etiologies of acquired PRCA are manifold: exogenic triggers include drugs (recombinant human erythropoietin; EPO), infections, and ABO-incompatible bone marrow transplantation [7, 8]. Parvovirus B19 and Epstein-Barr virus infection have been associated with PRCA [6], and recently, a case report was published by Karrat and Eddou on a 77-year-old male who developed PRCA after COVID-19 infection and responded well to standard treatment of steroids [9].

PRCA is a rare manifestation of autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, and others [10, 11]. Malignancies include hematological malignancies such as chronic lymphocytic leukemia (B-cell, T-cell, or large granular lymphocyte LGL), lymphomas, and solid tumors, mainly thymoma [12], and pregnancy rarely induce PRCA [4]. There is not enough information in the literature on the percentage of the different primary causes of PRCA.

Table 106.1 Classification of acquired adult PRCA by associated disease

Primary pure red cell aplasia	
Secondary red cell aplasia	
1. Exogenic triggers	I. Drugs: Recombinant human erythropoietin, phenytoin, trimethoprim-sulfamethoxazole, zidovudine, chlorpropamide, mycophenolate mofetil
	II. Infections: B19 parvovirus, human immunodeficiency virus, viral hepatitis, Epstein–Barr virus
	III. ABO-incompatible bone marrow transplantation
2. Autoimmune diseases	Systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, Sjogren's syndrome, autoimmune hemolytic anemia
1.3. Malignancies	I. Hematological malignancies: Chronic lymphocytic leukemia (B-cell, T-cell, large granular lymphocyte type), lymphoma, myeloma, chronic myeloid leukemia, agnogenic myeloid metaplasia with myelofibrosis, prodrome of myelodysplastic syndrome
	II. Solid tumors: Thymoma, adenocarcinoma of the breast, squamous cell carcinoma of the lung
4. Pregnancy	

Pathophysiology of PRCA

The mechanism of B19 parvovirus-induced PRCA is by direct damage. The virus destroys proerythroblasts by attacking the blood group P antigen receptor. Severe anemia usually occurs in patients with hemolytic anemia or immune-compromised patients [13]. Most of the other cases are immunologically mediated red cell aplasia. In vitro studies show that PRCA bone marrow responds to EPO or normal plasma, but incubation with the patient's plasma often causes inhibition in heme synthesis. The inhibitor disappears in PRCA remission [14].

Antibody-Mediated PRCA

IgG antibodies are complement-binding or directly cytotoxic to erythroblasts [15]. The antibodies inhibit burst-forming unit erythroid (BFU-E) and colony-forming unit erythroid (CFU-E) colony formation. In rare cases, EPO-specific antibodies were identified, mainly in epoetin 2 (Eprex)-induced PRCA [8]. Other targets are the EPO receptor or other red cell signaling pathway factors [1].

In EPO-induced PRCA, the underlying cause may be connected to the stabilizer polysorbate 80 in rubber-coated pre-filled syringes and poor handling of the needles, producing organic compounds that function as an adjuvant, resulting in anti-EPO antibodies. Over 200 dialysis patients treated with EPO 2 subcutaneously developed PRCA between 2001 and 2003. Afterward, the rate declined because of new instructions to prevent this complication [8].

T-Cell-Mediated PRCA

Lymphocytes from patients with PRCA secondary to chronic lymphocytic leukemia (CLL), lymphomas, thymoma, and infection with EBV and HTLV1 suppress erythropoiesis in colony assays [16]. Expansion of LGLs and LGL leukemia are most associated with PRCA [1].

Clinical Manifestations

Because the course of the disease is slow, symptoms of anemia appear only in an advanced stage. Physical examination reveals pallor and signs of anemia [15]. After long-term red cell transfusion and glucocorticoid therapy, physical findings compatible with hemosiderosis and iatrogenic cushingoid state appear. In secondary PRCA, the symptoms are usually consistent with the primary disease.

Laboratory Findings

A significant normocytic normochromic anemia, usually requiring recurrent blood transfusions, is found in PRCA patients. The blood smear reveals severe reticulocytopenia with an absolute count of reticulocytes of less than 10,000/μL. Bone marrow analysis depicts normal myelopoiesis, lymphopoiesis, and megakaryopoiesis but only a few erythroid precursors with diminished erythroblasts to less than 1% of nucleated cells [4]. Vitamin B12, folic acid, serum iron, transferrin, and ferritin levels are normal [15].

Differential Diagnosis

The differentiation of PRCA from other diseases associated with red cell aplasia is usually not difficult and is based on bone marrow findings (Table 106.2). In myelodysplastic syndrome (MDS) patients, the bone marrow usually reveals dysplastic features in two or more blood lineages. Moreover, the marrow is hypercellular. Cytogenetic abnormalities are frequent in MDS. In aplastic anemia, pancytopenia with hypoplasia or aplasia of all three lines is the hallmark in bone marrow. To exclude the diagnosis of lymphoid malignancies (B, T, or LGL CLL), immunophenotyping of the lymphocytes by flow cytometry or T-cell receptor gene rearrangement is performed [1, 4, 15].

In PRCA related to parvovirus B19 infection, giant proerythroblasts with vacuolated cytoplasm and pseudopodia exist in the bone marrow. Elevated titers of IgM antibodies confirm the diagnosis. Still, in chronic conditions in an immune-compromised host, further diagnosis is needed to demonstrate the presence of viral DNA in the serum [1]. A chest CT scan is mandatory to exclude thymoma [12].

Diagnostic Criteria

The diagnosis of PRCA is established in severe normochromic normocytic anemia, with reticulocytopenia and almost complete absence of erythroblasts in the bone marrow with normal development of myeloid and megakaryocytic lines. There are no formal validated diagnostic criteria based on studies reporting sensitivity and specificity because PRCA is a rare disease with heterogeneous etiologies.

Table 106.2 Diagnostic procedures in acquired PRCA

	PRCA	Other diseases
Blood smear	Normocytic normochromic anemia, normal white cells, and platelets	– MDS: macrocytic anemia, dysplastic features of white cells, sometimes monocytosis or Pelger–Huët anomaly – Aplastic anemia: pancytopenia – CLL: lymphocytosis
Bone marrow biopsy	Less than 0.5–5% erythroblasts with normal myeloid and megakaryocytic lines	– MDS: hypercellular with dysplastic myelopoiesis, shift to the left, and “blasts and mononuclear megakaryocytes – Erythroblasts >5% with megaloblastoid features. Aplastic anemia: hypoplasia or aplasia of all three lines – Parvovirus B19: giant proerythroblasts with vacuolated cytoplasm and pseudopodia
Reticulocyte count	Less than 1%	– Usually more than 1%, except for aplastic anemia
Vitamin B_{12}, folic acid	Usually normal	–
Erythropoietin serum level	Elevated, except in the presence of anti-erythropoietin antibodies	–
Cytogenetic tests	Normal	– MDS: frequent abnormalities
Immune phenotyping of lymphocytes	Normal	– CLL: monoclonal proliferation
Parvovirus B19, IgM, PCR, or viral DNA	Negative IgM	– Parvovirus: Elevated IgM in immune-compromised patients: PCR or viral DNA detected
Chest CT scan	Normal	– Thymoma: mediastinal mass
Erythroid colony assay	CFU-E and BFU-E are usually present. In 60%, IgG in serum inhibits the growth of erythroid progenitors	–

BFU-E burst-forming unit erythroid, *CFU-E* colony-forming unit erythroid, *CLL* chronic lymphocytic leukemia, *MDS* myelodysplastic syndrome, *PRCA* pure red cell aplasia

Table 106.3 Diagnostic criteria for PRCA

1. Fall in red cell count of about 1%/day
2. Reticulocyte count below 1%
3. No significant changes in white cell count, platelet count, or differential leukocyte count
4. Normal cellularity of bone marrow, less than 1% erythroblasts (occasionally up to 5% proerythroblasts or basophilic erythroblasts)
5. Normal myeloid cells and megakaryocytes in bone marrow

Anemia + 4th and 5th criteria are sufficient for diagnosis

According to Casadevall et al., the standard diagnostic criteria for PRCA are listed in Table 106.3 [16]. In our opinion, anemia with the findings in the bone marrow of less than 1% erythroblasts with normal myeloid cells and megakaryocytes is sufficient for the diagnosis. It is required to exclude secondary PRCA according to the classification.

Therapy

According to clinical criteria, blood transfusions should be given for symptomatic anemia and supplemented with Vitamin B12 or folic acid in case of deficiency. Once the etiology is known, specific therapy should be given. Medications that might cause PRCA should be discontinued. Thymectomy is recommended in patients with thymoma. In cases of primary PRCA or secondary PRCA that are not responding to the therapy of the primary disorder, the recommended treatment is based on case series [15].

The first-line therapy is cyclosporine since it has a response rate of 70–75% compared to other treatments with a less than 40% response rate. The dose of cyclosporine is 2–6 mg/kg per day with a rapid taper. Corticosteroids may be used at high doses (prednisone at 30 mg/day) in combination with cyclosporine [4, 15].

This combination therapy is supported by the findings of Wu et al. [17], who reported a complete remission rate of 61.3% in the combination group compared to the 19.0% of the steroids group. These patients achieved remission faster with combination therapy than with only cyclosporine or steroids.

Other therapies that have been used include cyclophosphamide, azathioprine, cyclosporine, anti-thymocyte globulin, and a course of high-dose intravenous immunoglobulin (IVIg) [4, 15].

Therapies that have been reported in refractory cases include plasmapheresis and interferon. Reports of successful treatment in resistant PRCA include rituximab and alemtuzumab [15, 18], splenectomy and allogeneic stem cell transplantation after cyclophosphamide conditioning [19]. These therapies have been used in immunocompromised hosts, particularly in AIDS patients with chronic or severe cases of PRCA due to parvovirus infection.

Prognosis

Five to ten percent of patients remit spontaneously. Most patients (68%) enter remission with the standard immunosuppressive therapy, but up to 80% are at risk of relapse in 2 years; some will need low-dose maintenance immune suppressive treatment for 1–2 years. The estimated median survival of primary PRCA patients is 14 years [20]. Refractory cases diagnosed as primary PRCA may develop leukemia, usually the LGL type. The prognosis of secondary PRCA depends on the prognosis of primary disease [1].

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Autoimmune Neutropenia

107

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Abstract

Neutropenia is defined by a reduction in circulating polymorphonuclear neutrophils (PMNs) below 1.5 × 10^9/L, often resulting from autoimmune mechanisms involving the destruction of neutrophils by autoantibodies. Primary autoimmune neutropenia is more common in women and can manifest in infancy, while secondary cases often occur in adults with underlying connective tissue diseases or hematological neoplasms. Clinical presentation varies, and the risk of infections increases with the degree and duration of neutropenia. Laboratory findings include neutropenia, often with anemia, thrombocytopenia, and bone marrow abnormalities. Various serological tests are used to detect anti-neutrophil autoantibodies, with novel techniques like flow cytometry and enzyme-linked immunosorbent assays being developed. Treatment options are limited, with granulocyte colony-stimulating factor (G-CSF) being the primary therapy, but should be restricted to patients with a total absence of PMNs and severe infections.

Keywords

Polymorphonuclear neutrophil · Autoantibody

Neutropenia denotes a blood polymorphonuclear neutrophil (PMN) count below 1.5 × 10^9/L for at least 6 months. This disorder is autoimmune when the excessive destruction of PMNs proceeds from harnessing their plasma membrane with antibodies (Abs). Given the controversy over the role of immune complexes (ICs), such auto-Abs have, however, proved extremely difficult to be charged with the pathophysiology of the disease [1].

Primary autoimmune neutropenia (AINs) occurs as an isolated clinical entity, especially in infancy, where the frequency is 1 in 100,000 newborn babies [1]. It is more frequent in women and can be accompanied by other hematologic manifestations such as thrombocytopenia and anemia. In 36% of patients, anti-PMN antibodies have been found [1]. Secondary AINs are more common in adults and set against a background of connective tissue disease, e.g., primary Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA), or a background of hematological neoplasms, e.g., large granular lymphocyte (LGL) leukemia, autoimmune lymphoproliferative syndrome (ALPS), and even Hodgkin's disease. In the case of SLE, AIN has been associated with the disease's activity and found to be associated with a predisposition to infections [1]. Insights have recently been gained into the pathogenesis of these confusing settings.

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Pathogenesis

Approximately one-third of adult patients [1] and almost 80% of newborn babies with AIN [2] present with anti-PMN Abs in their serum. These auto-Abs must be set apart from Fc-gamma receptor (FcγR)II and FcγRIIIb-bound ICs in the former population and from neonatal alloimmune Abs in the latter. The antigens in the neutrophil membrane have been classified into five groups of antigenic systems called human neutrophil alloantigen (HNA) antibodies (HNA-1 to HNA-5) with seven antigens and a specific glycoprotein for every antigen [3]. Consistent with the heightened number of apoptotic PMNs in the circulation of patients with SLE [4], this source might be the release of antigens (Ags) by injured cells. There is no definite evidence of cell destruction's exact mechanism and location. Unlike autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura, where complement-mediated or Ab-dependent cell cytotoxicity operates, these anti-PMN Abs generate opsonic activity favoring the phagocytosis of sensitized cells by the reticulo-histiocytic system. However, although the patients show features of a survival defect, the degree of neutropenia does not square with the level of auto-Ab. Not only is the clearance of PMNs offset by a commensurate rise in the production of PMNs, but such a response can also be inverted. That is, a subset of anti-PMN Abs can rescue senescent cells from spontaneous apoptosis through the synthesis of granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor and the resulting downregulated expression of Bax in PMNs [5].

Clinical Presentation

The clinical course of primary AIN is relatively benign. AINs occur much more frequently than initially stated because of two biases. On one side, an asymptomatic individual does not give rise to investigation. Conversely, PMN counts vary daily, so cases described as cyclic neutropenia are possibly AINs [6]. Conversely, an average PMN count can be maintained, despite the presence of anti-PMN auto-Ab, through accelerated turn-over of the cells. Auto-Abs may, however, lead to qualitative defects by impairing the function of the cells [7].

It has been recognized that the degree and length of neutropenia augment the risk of infection. The most frequent complications are listed in Table 107.1. Various Gram-positive and Gram-negative bacterial infections and fungal infections with Candida and Aspergillus have been reported in infants [8] and adults [2]. In secondary AINs, infections have worsened during relapse of the underlying pathology. Concerning autoimmune settings, the messages are that neutropenia is rarely seen in patients with primary SS [1], detected in up to half of those with SLE [9], and associated with RA and variable splenomegaly [10] in Felty's syndrome (FS). AIN can also coexist with hematological diseases, and one-fourth of the LGL leukemia patients who experience RA resemble those with FS [11]. There is an obvious need for clarification of the relationship between these two diseases because they are distinguished by T-cell clonality, which exists in LGL leukemia but not in FS [12]. The clinical features in common are presented in Table 107.2. Notably, rheumatologic manifestations are more severe in FS than in RA. Another condition associated with PMN and platelet auto-Abs is ALPS [13]. In this intriguing disease, it is uncertain why blood cells are a common target for anti-self-responses, not the various organ systems, as seen in RA or SLE.

Table 107.1 Infections present at the time of diagnosis

Infection	Frequency (%)
Upper respiratory infections	20
Otitis media	17
Pyoderma	12
Fever of unknown origin	12
Abscess	10
Gastroenteritis	10
Pneumonia	8

Table 107.2 Clinical features associated with large granular lymphocyte leukemia

Clinical feature	Frequency (%)
Age > 50 years	70
Male: female	1
Recurrent infection	20–40
Splenomegaly	20–50
Fever, night sweats, and weight loss	20–30
Bone marrow involvement	25–80
Hepatomegaly	<20
Lymphadenopathy	<5

Hematological Findings

Laboratory findings are summarized in Table 107.3. Around 60% of the patients have isolated neutropenia, while 40% combine it with anemia and thrombocytopenia [3, 8]. Most show normal or increased cellularity in the bone marrow (BM), with an average or low number of mature PMNs. Phagocytosis of PMNs by BM macrophages is occasionally observed.

Table 107.3 Hematological features in primary autoimmune neutropenia

Finding	Frequency (%)
Isolated neutropenia	60
Neutropenia + anemia and/or thrombocytopenia	40
Normal bone marrow	30
Reduced no. of mature neutrophils	15
Hypercellular with reduced no. of mature neutrophils	20

Serological Tests

Several assays have been devised since no single method can pick up all possible anti-PMN auto-Abs. The screening procedure should include a minimum of two of them [14]: viz. the granulocyte agglutination test (GAT) and the granulocyte immunofluorescence test (GIFT), both based on the use of PMNs from blood donors as the substrate. Formal quality assurance schemes have recently confirmed that, although the GAT has low sensitivity compared with the GIFT, it is the only reliable method for detecting PMN-specific auto-Abs [15]. Most of them act against human neutrophil Ags (HNA) HNA-1a, HNA-1b, and HNA-1c on FcγRIIIb referred to as CD16, FcγRII referred to as CD32, complement receptor one referred to as CD35, and HNA-4a and HNA-4b on CD11b and CD11a, respectively [10, 16]. Recourse to the monoclonal Ab immobilization of granulocyte Ag assay is indicated in cases with complex mixtures of Abs or in which confirmatory tests are required [16].

PMN Abs have also been detected using an indirect immunofluorescence flow (IIF) cytometric test, coupled with an enzyme-linked immunosorbent assay (ELISA) with recombinant FcγRIIIb as a capture agent; such auto-Abs have been detected in half of the patients with primary SS, and the sera categorized based on positivity for the two methods as IIF (+) / ELISA (+), IIF (+) / ELISA (-) and IIF (-) / ELISA (+) [17]. Their presence does not necessarily imply that the patients are neutropenic. More recently, auto-Abs to myeloid precursors have been recognized in pure white-cell aplasia [18], and auto-Abs against G-CSF were identified in neutropenic patients with SLE or FS [19]. In some other patients, there is evidence for anti-Ro/Sicca syndrome A cross-reacting with PMN membrane Ags in patients with SLE or primary SS [19].

Therapy

Steroids exert little effect. To date, G-CSF is the sole therapy allowing recovery of the circulating PMN count and better control of infection in primary AIN and FS. This treatment should be more restricted to cases with severe infections, that RA and SLE patients can flare on G-CSF. Remission was also obtained using the humanized monoclonal anti-CD52 Ab Campath-1 H. Parenthetically, although it can induce neutropenia, intravenous immunoglobulin has met transient remission. It stands to reason that control of the underlying disease in secondary AINs is of utmost importance in secondary AINs.

Until now, there have been no diagnostic criteria for AIN; the finding of indirect anti-PMN antibodies has a sensitivity of 74% [20]. Nevertheless, it is recommended to accept it as AIN If all other causes have been excluded.

In conclusion, there is a need for standardization of the tests for anti-PMN auto-Abs. These may accompany numerous pathological settings, such as BM or organ transplantation, Rituximab or fludarabine treatment, parvovirus B19, or human immunodeficiency virus infection. Still, several issues remain areas of intense investigation.

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Immune Thrombocytopenia

108

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Abstract

Immune thrombocytopenia (ITP) is an acquired thrombocytopenia, defined as a platelet count <100,000/μL, caused by immune destruction of platelets. The reduced peripheral blood platelet count results from premature destruction and a relative inadequacy of platelet production. ITP occurs in people of all ages, with around 40% of cases affecting children under ten. Approximately 80% of children with ITP present with an acute, self-limiting form of the condition. Adults more commonly develop the chronic form of ITP, resulting in a higher prevalence among those over 60 years of age. An estimated 50% to 70% of adults with ITP have the chronic form.

The diagnosis of ITP is based principally on excluding other causes of isolated thrombocytopenia using patient history, physical examination, blood count, and evaluation of the peripheral blood smear. No "gold standard" test exists to establish the diagnosis reliably.

The first line of treatment includes corticosteroids such as dexamethasone. Second-line medical therapies include thrombopoietin receptor agonists (TPO-RAs), rituximab, fostamatinib, and other immunosuppressive drugs.

Keywords

ITP · Bleeding disorder · Platelet antibodies

Definition

Immune thrombocytopenia (ITP) is an acquired thrombocytopenia, defined as a platelet count <100,000/μL, caused by immune destruction of platelets [1]. It was formerly known as "idiopathic thrombocytopenic purpura." Still, in 2019, the International Working Group on ITP (IWG) recommended that this disease should be named "Immune Thrombocytopenia" (retaining the abbreviation ITP); this terminology recognizes the immune pathogenesis of ITP and the fact that patients with ITP may not uniformly exhibit purpura or bleeding manifestations [2].

The reduced peripheral blood platelet count results from premature destruction and a relative inadequacy of platelet production. In addition to antibody-mediated platelet destruction, which has been recognized since the 1950s, other mechanisms are involved. These include T-cell-mediated apoptosis of megakaryocytes, inhibition of platelet production, and T-cell destruction of platelets. The underlying pathophysiology is better understood today and has led to the development of new treatments [3]. ITP remains a diagnosis of exclusion; there should be no detectable underlying cause for the thrombocytopenia found on investigation. ITP with an underlying cause is termed secondary ITP [4].

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Epidemiology

The annual incidence of ITP is approximately 5 cases out of every 100,000 children and 2 cases per every 100,000 adults [5]. ITP occurs in people of all ages, with around 40% of cases affecting children under 10 years of age. Approximately 80% of children with ITP present with an acute, self-limiting form of the condition, which resolves within 12 months; it often resolves much sooner, sometimes as early as 3 months after onset. The other 10% to 20% of children develop the chronic version of ITP, which lasts more than 12 months [6]. Adults more commonly develop the chronic form of ITP, resulting in a higher prevalence among those over 60 years of age. An estimated 50% to 70% of adults with ITP have the chronic form [5].

Classification

In 2019, the IWG established a nomenclature in which ITP was classified according to the duration of the disease and into severe or refractory forms; Table 108.1 shows this classification. On the other hand, the American Society of Hematology also proposed a nomenclature classifying ITP according to platelet count; this classification is illustrated in Table 108.2.

Table 108.1 Classification of Immune thrombocytopenia

Newly diagnosed	Duration: <3 months
Persistent	Duration: 3–12 months
Chronic	Duration: >12 months
Severe	Clinically relevant bleeding of sufficient magnitude to mandate treatment or require additional interventions or an increase in drug dose
Refractory	Presence of severe ITP after splenectomy

Taken from Ref. [4]

Table 108.2 Classification for immune thrombocytopenia from the American Society of Hematology

Corticosteroid dependent	There is an ongoing need for continuous prednisone >5 mg/d (or corticosteroid equivalent) or frequent courses of corticosteroids to maintain a platelet count >30,000 and to avoid bleeding
Remission	Platelet count 100,000 at 12 months
Early response	Platelet count >30,000 and at least doubling baseline at 1 week
Initial response	Platelet count >30,000 and at least doubling baseline at 1 month

Taken from Ref. [7]

Pathogenesis

Primary ITP

It has been 70 years since the famous Harrington-Hollingsworth experiment showed that plasma from patients with ITP caused significant thrombocytopenia when infused into healthy volunteers [3]. In the last few years, our understanding of the pathophysiology of ITP has significantly improved. Primary ITP is an acquired immune disorder where thrombocytopenia results from pathological antiplatelet antibodies, impaired megakaryocytopoiesis, and T-cell-mediated destruction of platelets [1]. It now appears that B- and T-cell defects are a central feature of ITP pathophysiology, and the most compelling evidence is that a failure of self-tolerance mechanisms causes platelet autoimmunity [4].

Pathologic Antiplatelet Antibodies

As many as 60% to 70% of patients with ITP have platelet-specific immunoglobulin G antibodies (IgG). These are generally directed at the most abundant platelet surface glycoproteins, GPIIb/IIIa and GP1b/IX/V. The type of epitope targeted by these autoreactive antibodies may influence the course of the disease [1]. Splenic macrophages expressing FcγR internalize antibody-coated platelets, degrade them, and present platelet glycoprotein-derived peptides to autoreactive CD4 T cells interacting with B cells. This leads to somatic hypermutation and class switching. Autoreactive B cells differentiate into antiplatelet antibody-producing plasma cells that either stay in the spleen or migrate to the blood and bone marrow. Megakaryocytes in the bone marrow express platelet glycoproteins such as GPIIb/IIIa and GPIb/IX/V, and autoantibodies against these antigens impair platelet production and contribute to megakaryocyte apoptosis [7].

Defects in Antigen-Presenting Cells and T-Reg Deficiency

All IgG responses, including autoimmune IgG production in ITP, are initiated by T helper cells that recognize their cognate peptide antigens in association with major histocompatibility complexes (MHC) on antigen-presenting cells (APC) [3]. Catani et al. showed that DC-associated indoleamine 2,3-dioxygenase 1 (IDO1) was reduced in patients with ITP, and this was thought to impair the differentiation of regulatory T cells (T-regs), which contributes to the observed T-reg deficiency in ITP [8]. Hymes et al. [2] suggested that a defective CD8+ T cell suppression was responsible for the excessive production of anti-platelet autoantibodies. It took almost 27 years for the notion that lack of T-cell suppression was apparent in ITP when Liu et al. demonstrated that patients with ITP have defective and reduced numbers of CD4+ T regulatory cells, leading to the conclusion that ITP is due to a lack of peripheral T-cell tolerance mechanisms [9].

ITP and Complement

Activation of the classical pathway is implicated in the pathogenesis of ITP, with more severe disease occurring when low serum levels of C4 and C3 are accompanied by complement deposition on the surface of platelets [10]. Around 50% of ITP patients have antibodies that lead to the activation of the classical complement pathway generating C3a and C3b. The C3b deposited on platelets leads to subsequent platelet phagocytosis in the liver [10].

Secondary ITP

Secondary ITP is associated with other underlying disorders, such as autoimmune diseases (systemic lupus erythematosus or rheumatoid arthritis), HIV, Helicobacter pylori infection, or underlying immune dysregulation syndromes, such as common variable immunodeficiency [2]. Loss of peripheral tolerance may also be the cause of secondary ITP due to vaccines or infectious exposures such as the mumps-measles-rubella (MMR) vaccine, Helicobacter pylori infection, and infection with cytomegalovirus (CMV) or Varicella-Zoster virus (VZV). The most common disease associated with ITP is hepatitis C, which is present in up to 20% of ITP cases, with a higher incidence in some geographical regions [2].

Clinical Manifestations

Since ITP is mainly a diagnosis of exclusion, it is primarily seen in patients with a history of mucocutaneous bleeding, sudden petechial rash, and bruising. About 60% of children diagnosed with ITP have a preceding viral illness within the past month [6]. Thrombocytopenia is the sine qua non of ITP, and the diagnosis requires a platelet count <100,000/μL according to consensus guidelines. Many patients with ITP are asymptomatic; however, up to two-thirds may experience bleeding manifestations [7]. Bleeding is most significant at platelet counts less than 20,000 to 30,000/μL. Bleeding typically occurs in the skin or mucous membranes in a “platelet-type” pattern, with common petechiae, bruising, epistaxis, and gum bleeding. “Wet purpura” or hemorrhagic blisters on the mucous membranes, commonly in the oral cavity, can also occur and are often considered a harbinger of more severe bleeding [7]. Severe bleeding rates are more common in childhood compared to adult patients: a review by Neunert et al. showed that severe bleeding occurs in 20.2% of children and 9.6% of adults. The most severe bleeding event is ITP-associated intracranial hemorrhage (ICH): it represents a rare cause of pediatric stroke, affecting only 0.4% of children with ITP but with elevated mortality rates [11].

Most patients with chronic ITP with low platelet count do not bleed. Some with higher platelet counts bleed spontaneously and dangerously. There is no direct correlation between the platelet count and the severity of illness [12]. A systematic review found that 56% of patients with primary ITP experienced severe bleeding at some point during their disease course. Common bleeding categories included gastrointestinal hemorrhage, hematuria, ecchymosis, and epistaxis [12].

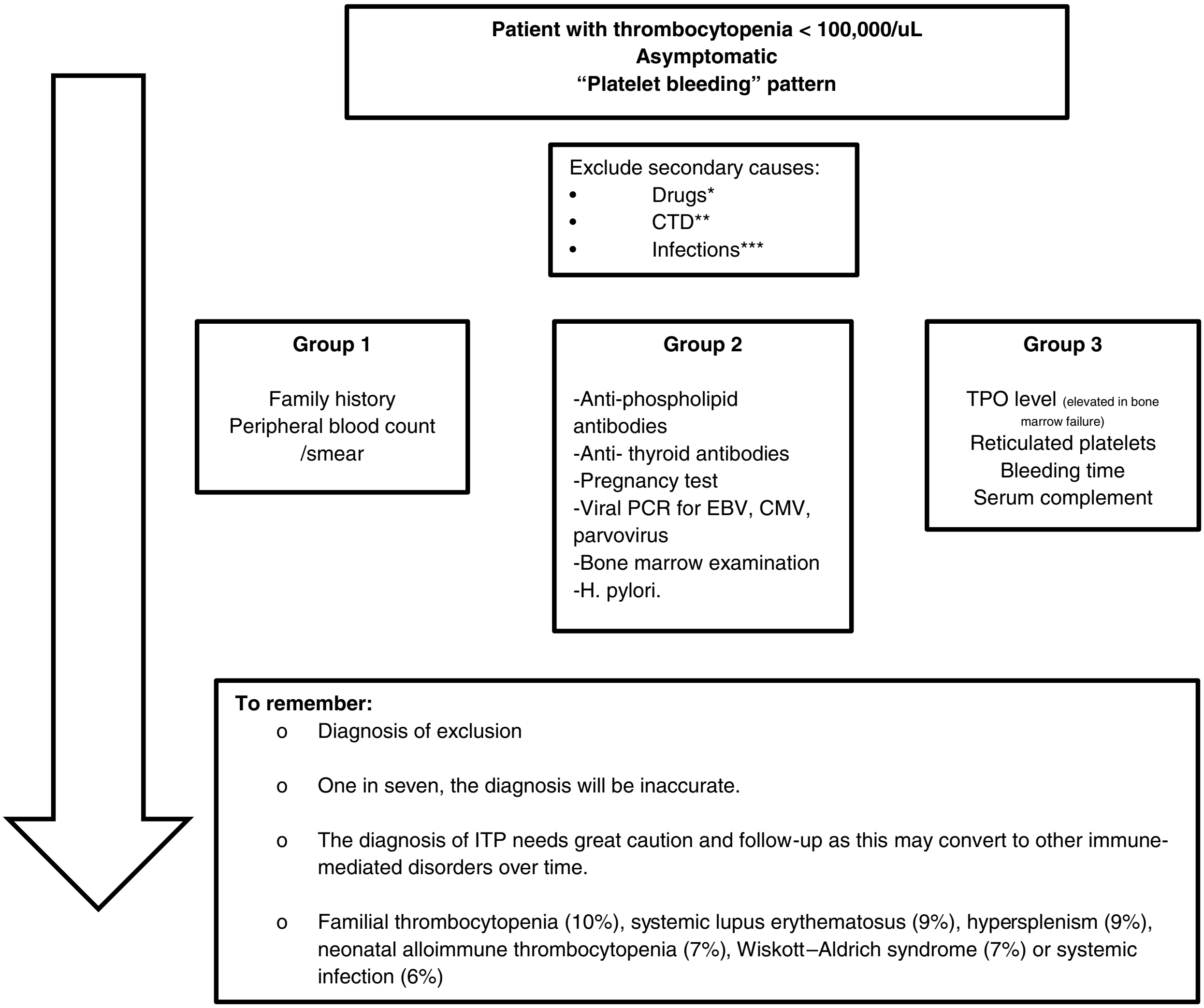
Fatigue is a commonly reported symptom in ITP and appears to correlate with thrombocytopenia, though it can be with mild to moderate thrombocytopenia. The cause of fatigue in ITP is unclear but has been attributed to the pro-inflammatory effects of immune dysregulation in ITP [7].

Diagnostic Criteria

The diagnosis of ITP is based on the exclusion of other causes of isolated thrombocytopenia using patient history, physical examination, blood count, and evaluation of the peripheral blood film (to exclude other hematological conditions, including hereditary thrombocytopenia and pseudo thrombocytopenia) [4]. Diagnostic tools for adults and children with suspected ITP are grouped into three sets of recommendations (Fig. 108.1) [4, 12].

No “gold standard” test exists to establish the diagnosis reliably. Response to ITP-specific therapy such as intravenous immunoglobulin (IVIg), intravenous anti-D immunoglobulin (IV anti-D-Ig), or steroids supports the diagnosis. Still, it does not exclude secondary ITP because many secondary ITPs respond to IVIg [4].

The recommendation from the IWG is to evaluate bone marrow in patients >60 years old with newly diagnosed ITP. In contrast, ASH guidelines suggest that bone marrow may not be necessary. Bone marrow examination may be informative in patients with systemic symptoms, abnormal signs, or suspicion of a different diagnosis [4]. Assays for antibodies to specific platelet glycoproteins are not routinely recommended; they have high specificity and low sensitivity but may be helpful in complex and challenging cases [13].


Patient with thrombocytopenia < 100,000/uL
Asymptomatic
“Platelet bleeding” pattern
Exclude secondary causes:
Drugs*
CTD**
Infections***
Group 1
Family history
Peripheral blood count /smear
Group 2
-Anti-phospholipid antibodies
-Anti- thyroid antibodies
-Pregnancy test
-Viral PCR for EBV, CMV, parvovirus
-Bone marrow examination
-H. pylori.
Group 3
TPO level (elevated in bone marrow failure)
Reticulated platelets
Bleeding time
Serum complement

To remember:

- Diagnosis of exclusion
- One in seven, the diagnosis will be inaccurate.
- The diagnosis of ITP needs great caution and follow-up as this may convert to other immune-mediated disorders over time.
- Familial thrombocytopenia (10%), systemic lupus erythematosus (9%), hypersplenism (9%), neonatal alloimmune thrombocytopenia (7%), Wiskott–Aldrich syndrome (7%) or systemic infection (6%)

Fig. 108.1 Diagnosis of immune thrombocytopenia. The approach to thrombocytopenia begins by excluding secondary causes. It starts with the tests in group 1 and moves on to the following groups if no diagnostic confirmation exists. *CTD* connective tissue disease, *TPO* thrombopoietin. * Drugs (prescription or nonprescription), including heparin, alemtuzumab, PD-1 inhibitors, abciximab, valproate, alcohol abuse, consumption of quinine (tonic water), exposure to environmental toxins, or chemotherapy. ** Systemic lupus erythematosus, or APS. ***Infections HIV, HCV, HBV

Prognosis

The prognosis for patients with immune thrombocytopenia varies depending on several factors, including disease type, response to treatment, age at disease onset, sex, and extremely low platelet counts, resulting in severe bleeding complications that can become life-threatening [3]. Over 80% of untreated children with acute ITP achieve clinical remission spontaneously, making a complete recovery with normal platelet levels within 2 to 8 weeks. A systematic review and meta-analysis identified the following factors associated with a higher risk of ITP in children becoming chronic [14]:

• Female sex (odds ratio [OR] 1.17)	• Age ≥ 11 years at presentation (OR 2.47)
• No preceding infection or vaccination (OR 3.08)	• Insidious onset (OR 11.27)
• Platelet count ≥20 × 10^9/μL at presentation (OR 2.15)	• Presence of antinuclear antibodies (OR 2.87)
• Treatment with methylprednisolone plus intravenous immunoglobulin (OR 2.67)	

Factors associated with lower likelihood of developing chronic ITP were as follows [14]:

- Mucosal bleeding at diagnosis (OR 0.39).
- Treatment with intravenous immunoglobulin alone (OR 0.71).

In adults, spontaneous remission occurs in less than 10%, one-third of patients undergo remission, and up to 75% improve within 5 years. However, many patients have mild and stable disease (i.e., platelet counts >30,000/μL with minimal or no bleeding; routine blood count often discovers them) [7].

Table 108.3 Treatment for ITP

Initial treatment	Corticosteroids	• Dexamethasone 40 mg/d for 4 days, repeated up to 3 times • Prednisone 1 mg/kg maximum 80 mg for 2 to 3 weeks • Methylprednisolone 30 mg /kg /day for 7 days
	IVIg	1 g/kg on 1 or 2 consecutive days
	Anti D	50–75 µg/kg once
Second-line treatment	Rituximab	Four infusions of 375 mg/m^2 or 1000 mg on days 1 and 15
	TPO-Ras	• Eltrombopag 25–50 mg/d • Romiplostim 1 µg/kg per week subcutaneously *(The median time to first response is 1 week)*
	Azathioprine	1–2 mg/kg maximum 150 mg/day 3–6 months
	Danazol	200 mg 2–4 times daily for 3–6 months
	Mycophenolate mofetil	1.5 g—2 g/day for at least 12 weeks
	Surgical therapies	Splenectomy: It is recommended to wait at least 12 to 24 months from diagnosis before performing splenectomy due to the possibility of remission or stabilization of platelet count at a hemostatic level
Third-line treatment	Alemtuzumab	10 mg subcutaneously on days 1–3 in combination with rituximab
	Combination of initial and second-line therapies Hematopoietic stem cell transplantation	

Taken from Ref. [4]

Therapy

The primary focus of management is the prevention of bleeding and patient safety by elevating the patient's platelet count to 20–30 × 10^9/µL. The goal of "safety" rather than normalization of the platelet count was outlined many years ago by Karpatkin [3]. The most common treatment is immunosuppression using corticosteroids, azathioprine, mycophenolate, cyclosporin A, and rituximab [3] (Table 108.3).

Asymptomatic patients with a platelet count >30,000/µL and no bleeding do not require treatment and can monitored. Adults with newly diagnosed ITP with bleeding and a platelet count <30,000/µL are usually given an oral corticosteroid (prednisone 1 mg/kg orally once a day or dexamethasone 40 mg orally once a day for 4 days) [11]. Second-line therapies include thrombopoietin receptor agonists (TPO-RAs), rituximab, fostamatinib, or other immunosuppressive drugs [11].

In children or adults with life-threatening bleeding, rapid phagocytic blockade is attempted by giving intravenous immunoglobulin (IVIg) 1 g/kg once a day for 1 to 2 days or, in Rh-positive patients, a single dose of IV anti-D-Ig 75 µg/kg. IV anti-D-Ig is only effective in patients who have not had a splenectomy and may be associated with severe complications such as severe hemolysis and disseminated intravascular coagulation [4]. High-dose methylprednisolone (1 g IV once a day for 3 days) is more accessible than IVIg or IV anti-D-Ig but may not be as effective. Patients with ITP and life-threatening bleeding are also given platelet transfusions but are not used prophylactically [11].

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15.

Thrombotic Thrombocytopenic Purpura and Other Thrombotic Microangiopathic Hemolytic Anemias

109

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Abstract

Thrombotic microangiopathies (TMA) are a group of disorders characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and microthrombi leading to ischemic tissue injury. The classification of the TMAs is challenging and constantly evolving with a greater understanding of the molecular basis of the disease. These disorders can be divided into primary or secondary forms. Primary thrombotic microangiopathies occur spontaneously with no associated underlying cause. Secondary forms arise in the context of another disease or trigger, like autoimmune disease, medications, etc. Though rare, thrombotic microangiopathies are life-threatening conditions that require urgent management.

Since 2001, ADAMTS13 has been identified as the main factor in the pathogenesis of TTP. Therefore, point-based TTP prediction scores have been validated to predict an acquired ADAMTS13 deficiency. These scores include platelet count, serum creatinine level, and either detectable antinuclear antibodies or D-dimer, reticulocytes, and indirect bilirubin. As these standard investigations are not specific for TTP and may be present in the miscellaneous differential diagnosis for TTP, they should be complemented by analysis of ADAMTS13, the unique marker sensitive and specific for TTP.

With prompt therapeutic plasma exchange (TPE) initiation, the average survival rate from the first episode of TTP is 80% to 90%. Long-term follow-up of patients with TTP, including medical consultation, standard biology, and ADAMTS13 activity monitoring, is also justified by the relapsing risk of this disease.

Keywords

Thrombotic thrombocytopenic purpura · Hemolytic uremic syndrome · Thrombotic microangiopathies · ADAMTS13 · von Willebrand factor

Definition

Thrombotic microangiopathies (TMA) are a group of disorders characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and microthrombi leading to ischemic tissue injury. Microangiopathic hemolytic anemia is the hallmark of thrombotic microangiopathy. It is a

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descriptive term for non-immune hemolysis resulting from intravascular red blood cell fragmentation that produces schistocytes on the peripheral blood smear. Characteristic laboratory data are a negative direct antiglobulin (Coombs) test, an increased lactate dehydrogenase (LDH), increased indirect bilirubin, and low haptoglobin [1]. TMA is a pathologic diagnosis made by tissue biopsy, typically a kidney biopsy, and it is commonly inferred from the observation of MAHA and thrombocytopenia due to platelet activation and consumption [2]. Not all episodes of MAHA are caused by a TMA, and not all TMA will present with MAHA and thrombocytopenia. For example, some syndromes present with TMA are limited to the kidney [3].

Classification

The classification of the TMAs is challenging and constantly evolving with a greater understanding of the molecular basis of the disease. These disorders can be divided into primary or secondary forms. Primary thrombotic microangiopathies occur spontaneously with no associated underlying cause. Secondary forms arise from another illness or trigger, like autoimmune disease, medications, etc. [4]. Table 109.1 shows the classification of TMAs.

Epidemiology

Though rare, thrombotic microangiopathies are life-threatening conditions that require urgent management. The incidence of TTP is much greater in adults (2.9 cases per one million per year) than in children (0.1 cases per one million per year). Factors that are associated with an increased frequency of this disorder include an age of 18 to 50 years, black race, and female sex [2]. The peak incidence is in the fifth decade in the United States; meanwhile, in Europe, the peak incidence is in the third decade. Pregnant women and children are much more likely to show a genetic (congenital) cause for TTP than other patients [5].

Hemolytic uremic syndrome (HUS) had an annual crude incidence of 0.66 per 100,000 people. Females were more likely than males to develop HUS, but only marginally more frequently. Patients under 20 years old are the age group where HUS is most common. The atypical-HUS annual incidence in the 20-year-old or younger age group ranged from 0.26 to 0.75 per million population. For all ages, yearly incidence ranged from 0.23 to 1.9 per million [6]. Epidemiology is not well known for the rest of the TMA's due to the rarity of the diseases. When reported, incidence and prevalence estimates are often combined, leading to inaccurate estimates of individuals diagnosed.

Table 109.1 Classification of thrombotic microangiopathies [2, 4]

Primary		
		Investigation test
TTP	Congenital "Upshaw–Schulman syndrome"	Mutations of *ADAMTS13* gene
	Acquired	ADAMTS13 activity and inhibitor
HUS	STEC-HUS	PCR for the Shiga toxin, or stool culture for STEC or Shigella
	Atypical HUS	Genetic mutations in complement regulatory proteins
Metabolism mediated- TMA.	Homozygous mutations in MMACHC (encoding methylmalonic aciduria and homo-cystinuria type C protein)	
Coagulation-mediated TMA	Homozygous mutations in diacylglycerol kinase ε and mutations in plasminogen and thrombomodulin were also implicated.	
Secondary		
• Malignant hypertension • Pregnancy-associated thrombotic microangiopathy, preeclampsia/ eclampsia, HELLP • Drugs and toxins (e.g., calcineurin inhibitors, quinine, ticlopidine) • Infections (e.g., influenza, HIV, Epstein–Barr virus, parvovirus) • Autoimmune disease (e.g., systemic lupus erythematosus, catastrophic antiphospholipid syndrome, scleroderma renal crisis) • Transplantation (e.g., solid organ, bone marrow)		

History

TTP was the first clinical and pathological description of thrombotic microangiopathy in 1924 by Eli Moschovitz as "an acute febrile pleomorphic anemia with hyaline thrombi in arterioles and capillaries" [2]. In 1982, Moake postulated the link between TTP and the von Willebrand factor (VWF). He found that the plasma of patients with chronic relapsing TTP contained ultra-large VWF (ULVWF) multimers and hypothesized that deficiency of depolymerase was responsible for the ULVWF multimers [2]. In 1998, patients with idiopathic TTP were reported to develop autoantibodies against VWF-cleaving protease, but in children with congenital TTP, the activity of this metalloprotease was absent [4]. In 2001, Zheng et al. identified the protease as a new member of "a disintegrin and metalloprotease with thrombospondin type 1 motif" (ADAMTS13), which participated in the pathogenesis of TTP. At the same time, Levy et al. identified the ADAMTS13 locus to chromosome 9q34 by pedigree analysis in families suffering from congenital TTP and defined 12 mutations in the ADAMTS13 gene. Congenital TTP often presents in childhood but can manifest for the first time after a "second hit" later in life; for women, this can occur during or immediately after pregnancy [5, 7].

Pathogenesis

Acquired and Inhered TTP

A severe functional ADAMTS13 deficiency causes the blood accumulation of platelet-hyper adhesive ultra-large VWF multimers, forming platelet-rich microthrombi within small arterioles. In most cases, the mechanism for ADAMTS13 severe deficiency is acquired via autoantibodies to ADAMTS13, as demonstrated by positive anti-ADAMTS13 IgG in 75% of TTP during an acute phase [8].

Anti-ADAMTS13 autoantibodies are primarily divided into two categories: inhibitory and non-inhibitory. Inhibitory antibodies neutralize the proteolytic activity of ADAMTS13, and non-inhibitory antibodies bind to the protease, accelerating its clearance from plasma. Anti-ADAMTS13 autoantibodies have been found against all domains of ADAMTS13, indicating a polyclonal immune response. However, the spacer domain of ADAMTS13 has been identified as an immunogenic region [5].

In addition to free anti-ADAMTS13 autoantibodies, immune complexes containing ADAMTS13 have also been found in 39–93% of patients during acute acquired TTP. Given that C3a and C5a are elevated during the acute TTP episode, this could suggest that the complement is activated through the classic pathway via ADAMTS13 antigen-antibody immune complexes. The clinical significance of complement activation in TTP is still unclear, though it further supports the "second hit" hypothesis that another physiologic stressor in conjunction with severe ADAMTS13 deficiency is required to induce the clinical syndrome [5].

These antibodies may not be detectable in 20% to 25% of acute TTP, raising the hypothesis that severe ADAMTS13 deficiency in these patients may result from different, as-yet-unclear mechanisms. Several hypotheses may explain ADAMTS13 severe deficiency in these cases: lack of sensitivity of anti-ADAMTS13 IgG assays in detecting IgG trapped within immune complexes, involvement of other Ig isotypes, decreased synthesis/secretion of ADAMTS13 (i.e., in acute liver insufficiency), degradation of ADAMTS13 by sepsis enzymes such as calpains, elastases, thrombin, or plasmin and catalytic inhibition of ADAMTS13 by free hemoglobin or interleukins [7].

Severe ADAMTS13 deficiency is the only causing factor for TTP identified so far. As mentioned above, although it is necessary to cause TTP, enzyme activity deficiency is insufficient to induce the clinical syndrome [12]. However, some clinical and laboratory features that correlate with ADAMTS13 deficiency may be considered as risk factors for acquired TTP (i.e., female sex, black ethnicity, HLA-DRB1*11, and obesity), whereas HLA-DRB1*04 is protective [9].

A last and rare (2% of all cases) mechanism for ADAMTS13 severe deficiency is genetic via recessively inherited biallelic mutations of the ADAMTS13 gene (patients are either homozygous or compound heterozygous), causing congenital TTP. About 150 distinct mutations of the ADAMTS13 gene are reported worldwide, with a low degree of overlap between the continents. These mutations are spread all over the ADAMTS13 gene, with most of them being located within the N-terminal region; they consist of 70% of missense mutations and 30% of truncating mutations (no total deletion of ADAMTS13 gene has ever been described) [8].

Typical and Atypical Hemolytic Uremic Syndrome

HUS is most caused by Shiga toxin (typical/STEC-HUS) or, less commonly, infections or genetic abnormalities activating the alternative complement pathway (atypical -HUS) [10]. Prior classifications of HUS often depended on the presence or absence of bloody diarrhea, with its presence used to diagnose typical HUS associated with Shiga toxin (ST). However, atypical HUS can also present with bloody diarrhea in up to 30% of cases, so an etiology-based classification system is preferred [11].

In the United States and Europe, the organism responsible for ST-HUS typically is an *Escherichia coli* such as O157:H7, O111, or O104:H4. *Shigella* species may be more common as a source of Shiga toxin in Asia. Once ingested, Shiga toxin-producing *Escherichia coli* (STEC) penetrates the mucous layer of the intestine and secretes ST, which binds to the receptor Gb3. The ST/Gb3 complex binds to cell ribosomes, inhibiting protein synthesis and causing apoptosis; inflammatory cytokines are also produced [10].

ST can activate the complement system by inhibiting complement factor H. Upon entering the bloodstream; ST persists in binding to cells via the Gb3 receptor, with the highest prevalence in the glomerular microvasculature. Endothelial damage is caused by (1) direct cytotoxicity of ST, (2) disturbance of the hemostatic pathway, (3) increased cytokine release, and (4) alternative pathway activation. This endothelial damage then initiates the pathology associated with TMA [10].

In atypical-HUS, genetic or acquired dysregulation of the complement alternative pathway is detected in 40–60% of patients with atypical-HUS, suggesting a genetic predisposition. This dysregulation is caused by mutations in genes that encode complement regulatory proteins, Factor H (FH), Factor I (FI), membrane cofactor protein (MCP), complement 3 (C3), Factor B (FB) or thrombomodulin, or presence of anti-FH antibody resulting in activation of the complement system [12]. The dysfunction in the complement cascade leads to complement deposition on endothelial cells, thickening of arterioles and capillaries, and endothelial swelling and detachment. Consequently, proteins and cellular infiltrates such as neutrophils, macrophages, and platelets accumulate on the cell surface, inducing a pro-thrombotic state [13].

Although many mutations are implicated in the pathogenesis, disease development is multifactorial. While an individual may carry a mutation, a trigger (second hit) is required for atypical HUS. Thus, atypical HUS may be triggered by pregnancy, viral infection, cancer, organ transplantation, and the use of certain medications [13].

Clinical Manifestations

TTP

The historical clinical pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia, neurological symptoms, and renal insufficiency that used to define TTP appears obsolete, as several cohort studies have demonstrated that these five symptoms were present in less than 10% of patients with an acute TTP. The almost constant signs of TTP remain severe thrombocytopenia (typically $<30 \times 10^9$/L) and microangiopathic hemolytic anemia characterized by schistocytes on the blood smear [5].

Symptoms related to organ ischemia/infarction mainly concern the brain (60% of patients have neurologic symptoms at presentation, with a broad range from headache and confusion to stroke, coma, and seizures). Heart ischemia is also frequent (25% of patients, ranging from isolated electrocardiographic abnormalities to myocardial infarction), as well as mesenteric ischemia (35%), causing abdominal pain and sometimes diarrhea. Renal manifestations consist mainly of an isolated proteinuria/hematuria; acute renal failure is unusual in TTP, with typically a serum creatinine level below 2 mg/dL at presentation [7]. However, acute renal failure may not exclude TTP diagnosis, as some studies involving patients with severe TTP have reported 10% to 27% acute kidney injury [5].

In addition to the microangiopathic hemolytic anemia and consumption of thrombocytopenia, classical parameters for hemolysis show a high reticulocyte count, an undetectable serum haptoglobin concentration, and an elevated lactate dehydrogenase (LDH) level, a marker for tissue damage. The presence of schistocytes on the blood smear with a confident threshold value of 1% is the morphologic hallmark of the disease [7].

Typical Hemolytic Uremic Syndrome

The typical patient is a child younger than 5 years old with painful diarrhea and abdominal cramping between 1 and 10 days (median 4 days) after exposure to STEC. Typically, a presentation of bloody diarrhea occurs around day 2 or 3 following exposure, with HUS onset developing 3 to 10 days after the start of diarrhea. Other common symptoms are vomiting (67%), fever (37%), and abdominal pain (29%) [14].

HUS symptoms include renal symptoms, such as anuria, oliguria, and fluid overload, and symptoms related to anemia, such as syncope, fatigue, and pallor. Petechiae and easy bleeding may be notable due to thrombocytopenia [10]. Identifying risk factors for severe disease and poor long-term outcomes would help manage STEC-HUS children. Young age (<3 years) and dialysis >10 days were risk factors for later renal sequelae [15].

Atypical Hemolytic Uremic Syndrome

Atypical HUS can present at any age and is of acute onset in 20% of cases. The clinical presentation depends upon the extent of microvascular injury, thrombosis, and ischemic injury to various organ systems. Atypical HUS presents as a systemic disease and extra-renal features are seen in 20%, and a catastrophic presentation with multi-organ involvement in 5% of patients [13].

Patients with atypical HUS present with hemolytic anemia (hemoglobin <10 g/dL), thrombocytopenia (platelets<150,000/mm^3), and impaired renal function. Renal impairment is frequent; the most common manifestations are proteinuria, hematuria, hypertension, and uremia. While proteinuria is typically mild, nephrotic range proteinuria may occur. Most patients require renal replacement therapy [13].

About 10–48% of patients with atypical HUS present with nervous system involvement, making it the most common extra-renal manifestation. Symptoms include irritability, drowsiness, convulsions, encephalopathy, diplopia, cortical blindness, hemiparesis, hemiplegia, stupor, and coma [16]. The clinical features are like arterial hypertension and steno-occlusive diseases. Magnetic resonance imaging of the brain reveals symmetrical and bilateral lesions in basal ganglia, brain stem, and deep white matter. Approximately 10% of patients show complications such as myocardial infarction, myocarditis, heart failure, cardiomyopathy, and occlusive coronary artery disease [13]. Rarely, children may present with gangrenous lesions of the fingers and toes. Ischemic changes are due to small vessel vasculopathy secondary to complement abnormalities. Pulmonary manifestations, chiefly pulmonary hemorrhage, and hypoxemia, are reported in patients with multi-organ failure [13].

Diagnostic Criteria (Fig. 109.1)

TTP

Point-based TTP prediction scores have been validated to predict an acquired ADAMTS13 deficiency. These scores include platelet count, serum creatinine level, and either detectable antinuclear antibodies or D-dimer, reticulocytes, and indirect bilirubin [11]. As these standard investigations are not specific for TTP and may be present in the miscellaneous differential diagnosis for TTP, they should be complemented by an analysis of ADAMTS13, the unique marker sensitive and specific for TTP [7]. The TTP diagnosis is confirmed if ADAMTS13 activity is less than 10%. Subsequent investigations focus on the mechanism for ADAMTS13 severe deficiency: assays for ADAMTS13 autoantibodies, ADAMTS13 inhibitors, and gene sequencing in selected cases [17].

Reference methods for ADAMTS13 activity remain homemade manual methods requiring substantial skill to provide enough reliability for diagnostic use. Consequently, these reference methods are limited to expert laboratories. Rapid commercial ELISA assays for ADAMTS13 activity manageable in local laboratories were recently developed, but they do not have the accuracy and reliability of the reference methods [18]. Urgent therapeutic management is usually decided based on TTP clinical symptoms and not on ADAMTS13 results. However, the ADAMTS13 investigation remains crucial to confirm TTP diagnosis [7].

HUS

ST-HUS diagnosis is based on clinical and lab findings following a history of prodromal diarrhea and confirmed by serological testing and positive microbiological cultures for Shiga toxin-producing E. coli. Other causes of TMA are considered if these tests are negative or without a history of diarrhea or bloody stools [13]. Distinguishing atypical HUS from TTP can prove challenging in adults. TTP is characterized by the triad of TMA with predominately neurologic features, as opposed to predominately renal impairment without neurologic symptoms in atypical HUS [13].

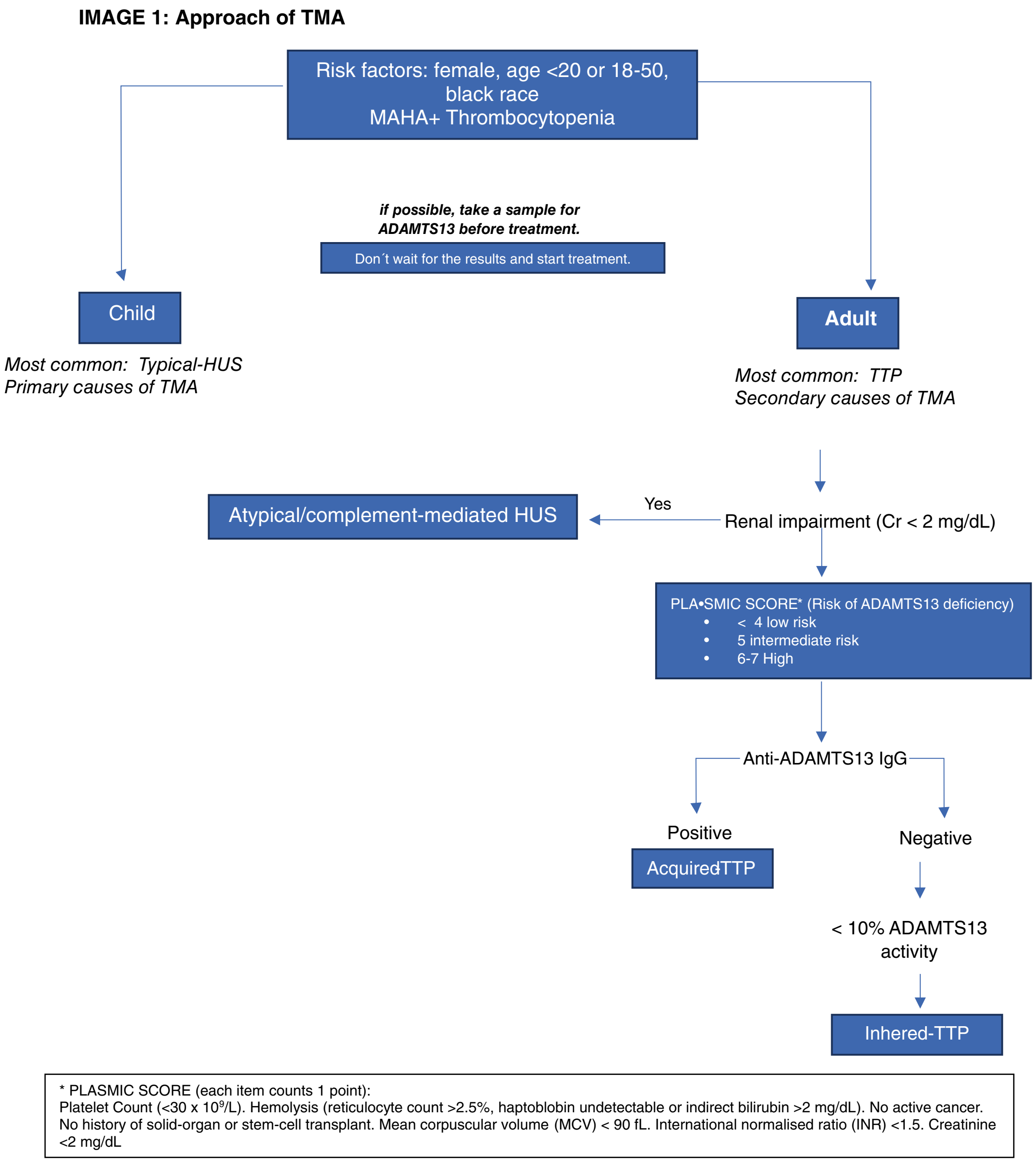
IMAGE 1: Approach of TMA
Risk factors: female, age <20 or 18-50, black race
MAHA+ Thrombocytopenia
if possible, take a sample for ADAMTS13 before treatment.
Don´t wait for the results and start treatment.
Child
Most common: Typical-HUS
Primary causes of TMA
Adult
Most common: TTP
Secondary causes of TMA
Atypical/complement-mediated HUS
Yes
Renal impairment (Cr < 2 mg/dL)
PLA•SMIC SCORE* (Risk of ADAMTS13 deficiency)
< 4 low risk
5 intermediate risk
6-7 High
Anti-ADAMTS13 IgG
Positive
AcquiredTTP
Negative
< 10% ADAMTS13 activity
Inhered-TTP

* PLASMIC SCORE (each item counts 1 point):
Platelet Count (<30 x 10^9/L). Hemolysis (reticulocyte count >2.5%, haptoblobin undetectable or indirect bilirubin >2 mg/dL). No active cancer. No history of solid-organ or stem-cell transplant. Mean corpuscular volume (MCV) < 90 fL. International normalised ratio (INR) <1.5. Creatinine <2 mg/dL

Fig. 109.1 Approach of TMA. * PLASMIC SCORE (each item counts 1 point): Platelet count (<30 × 10^9/L). Hemolysis (reticulocyte count >2.5%, haptoblobin undetectable or indirect bilirubin >2 mg/dL). No active cancer. No history of solid-organ or stem-cell transplant. Mean corpuscular volume (MCV) < 90 fL. International normalised ratio (INR) <1.5. Creatinine <2 mg/dL

Therapy

Plasma Exchange

Therapeutic plasma exchange (TPE) remains the cornerstone of the current management of TTP. TPE should be started as soon as the diagnosis of TTP is established or even suspected. TPE is performed daily until features related to organ involvement (cerebral manifestations, renal failure, increased troponin level, abdominal pain resulting from enteritis or pancreatitis) have resolved, the platelet count has stably recovered, and hemolysis has ceased [7].

Steroids

There is a rationale for the use of steroids in the treatment of acquired TTP, given its autoimmune nature. High-dose methylprednisolone (10 mg/kg/day for 3 days and then 2.5 mg/kg/day) may be more efficacious than standard-dose (prednisone: 1 mg/kg/day) as an adjunctive treatment to TPE in patients with newly diagnosed TTP [7].

Rituximab

The humanized anti-CD20 monoclonal antibody rituximab was first introduced in patients with a suboptimal response to TTP conventional treatment (i.e., disease exacerbation or refractoriness). The UK group reported in 2011 that frontline treatment with rituximab and TPE resulted in shorter hospitalization and fewer relapses that occurred later than a historical group not treated with rituximab. Therefore, it is a reasonable indication, although it may expose patients to overtreatment, as in up to 50% of cases, acquired TTP recovers with standard treatment. Further studies should determine whether rituximab improves the poorer outcomes of the more severe forms of the disease [7].

Caplacizumab

An inhibitor of VWF-glycoprotein 1b interaction (caplacizumab, formerly ALX-0081) was assessed in the TITAN trial, a multicenter, randomized, placebo-controlled phase 2 study in patients with acquired TTP. The time to platelet recovery was significantly shorter, and biomarkers reflecting ischemic organ damage tended to normalize more rapidly. Given that caplacizumab does not address the underlying autoimmune pathophysiology, there was a high rate of relapse after stopping caplacizumab 30 days after the last TPE session. Further studies are needed to assess the effectiveness [7].

Prognosis

With prompt TPE initiation, the average survival rate from the first episode of TTP is 80% to 90%. Older age; a very high lactate dehydrogenase (LDH) level (10 times the upper normal value), mainly reflecting organ damage; and an increased cardiac troponin level on diagnosis are associated with death and treatment refractoriness [18]. Patients with TTP are also prone (10%) to develop associated connective tissue diseases (mainly SLE and Sjögren syndrome), which require early identification during follow-up [7].

Long-term follow-up of patients with TTP, including medical consultation, standard biology, and ADAMTS13 activity monitoring, is also justified by the relapsing risk of this disease. In 40% of cases, patients with autoimmune TTP experience one or multiple relapses. Relapses result from severe ADAMTS13 deficiency caused by the persistence or recurrence of anti-ADAMTS13 antibodies. So far, ADAMTS13 is the only specific biological marker able to predict TTP relapses during the follow-up in clinical remission [7].

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110

Heparin-Induced Thrombocytopenia

Joan Carles Reverter and Dolors Tàssies

Abstract

Heparin-induced thrombocytopenia (HIT) is an acquired hemostasis disorder due to an immune response to the presence of platelet factor 4 (PF4)-heparin complexes. HIT is characterized by thrombocytopenia, which may be associated with severe thrombosis, developed in association with heparin treatment or exposure. HIT is caused by activation of platelets by PF4-heparin-IgG immune complexes. The diagnosis of HIT is based on clinical criteria confirmed by specific laboratory tests to identify anti-PF4 antibodies capable of activating platelets in the presence of heparin. The aim of this chapter is to outline the clinical and laboratory data used for the diagnosis of HIT.

Keywords

Heparin · Platelet factor 4 (PF4) · Heparin-induced thrombocytopenia (HIT) · Thrombocytopenia · Thrombosis

Introduction

Heparin-induced thrombocytopenia (HIT) is an autoimmune disorder consisting of the development of thrombocytopenia with normal or increased thrombopoiesis during heparin therapy [1–3]. It can be associated with thromboembolic complications without usually leading to hemorrhagic events. HIT is triggered by exposure to heparin, both unfractionated heparin (UFH) and low molecular weight heparin (LMWH).

HIT appears in temporal correlation with heparin therapy, presenting as unexplained thrombocytopenia or thrombocytopenia complicated by thrombosis [1, 4, 5]. The association of HIT with severe clinical thrombotic manifestations distinguishes HIT from other common drug-induced thrombocytopenias [6–10].

This chapter will focus on the clinical and laboratory diagnosis of HIT and the position of HIT among the broader concept of anti-PF4 syndromes.

Types of HIT

There are two types of HIT: Type I and Type II [4, 5].

Type I—This type of HIT is mediated by a non-immunological mechanism and does not cause thromboembolic complications or hemorrhagic manifestations. Type I HIT is usually associated with the use of high-dose heparin, thrombocytopenia is mild, platelets recover despite continued heparin therapy, and the clinical course is benign.

Type II—This type of HIT is immune-mediated and may be associated with generally severe thromboembolic complications but does not give hemorrhagic symptoms. Type II HIT is a severe disease requiring withdrawal of heparin and administration of an alternative (non-heparin) anticoagulant. In type II HIT, 30–70% of patients have thrombotic events, with a reported incidence of venous thrombosis three to four times more frequent than arterial thrombosis.

Table 110.1 shows the differences between Type I and Type II HIT.

Pathophysiology of HIT

The pathophysiology of type I HIT is not well understood. It is attributed to direct (non-immune-mediated) platelet activation, with mild thrombocytopenia and a benign clinical

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Table 110.1 Type I and type II heparin-induced thrombocytopenia

	Type I HIT (non-immune-mediated)	Type II HIT (immune-mediated)
Epidemiology	10–30% of heparin treated patients	Approximately 1% of patients treated with UFH and less common with LMWH
Temporal pattern	Starts in 1–4 days of initiating heparin	Starts in 4–16 days of initiating heparin
Severity of thrombocytopenia	Mild, usually platelet counts remain >100 × 10/L	Moderate to severe, usually less <100 × 10^9/L
Thrombosis	No	Yes
Spontaneous outcome	Spontaneous resolution without stopping heparin	Does not recover if heparin is not stopped

HIT heparin-induced thrombocytopenia

course [5]. It has been suggested that high doses of heparin cause platelets to bind to fibrinogen, resulting in thrombocytopenia.

Type II HIT is mediated by autoantibodies. In type II HIT, autoantibodies target a complex consisting of platelet factor 4 (PF4) and negatively charged glycosaminoglycans (GAGs) such as heparin and heparin-like molecules [4]. Platelet factor 4 is a normal cationic tetrameric platelet protein with a large amount of positive charge released from platelet alpha granules upon activation. When platelets are activated, a large amount of PF4 is released, and negatively charged heparin binds to the free positively charged PF4, causing changes in the configuration of PF4 to form ultralong PF4/heparin complexes (ULCs) [4]. Immune reactions can then be triggered by the activation of B lymphocytes by the ULCs. Activated B cells generate IgG1-based immune antibodies (IgG antibodies directed against ULCs) that conjugate with ULCs to form PF4-Heparin-IgG1 complexes. These immunocomplexes can lead to platelet activation by binding to FcγRIIa receptors (CD32) causing platelet aggregation [4]. The FcγRIIa receptor is a type I transmembrane glycoprotein that exists not only on the surface of the platelet membrane, but also on the surface of monocytes and endothelial cells. When this receptor binds to IgG antibody bound to ULCs, the immunoreceptor tyrosine-based activation motif (ITAM)-dependent signaling pathway will be activated to transmit signals that cause cell activation [4].

Monocytes also play an important role in the pathogenesis of thrombosis in type II HIT, as when monocytes are activated by PF4-Heparin-IgG1 complexes they produce a large number of tissue factor-bearing particles, which promote coagulation activation and thrombin formation [4]. Thrombin bound to these cell surfaces triggers a second activation signal to platelets via protease-activated receptor 1 (PAR-1), and activated platelets express phosphatidylserine promoting further thrombin generation. The second activation by PAR-1 enhances the effect of the first activation and induces aggregation of more platelets. PF4 released by activated platelets increases ULC and plays a positive feedback role in the development of HIT. In addition, PF4-Heparin-IgG1 complexes can also bind to FcγRIIa receptors on endothelial cells causing injury to the vascular bed. Taken together, this immune process promotes a hypercoagulable state with platelet activation and consumption leading to thrombocytopenia, and increased thrombin generation triggering thrombotic events [4].

Incidence of HIT

The frequency of occurrence of HIT depends on the origin of the heparin (more frequent in bovine than in porcine heparin), the length of the molecule (more frequent in UFH than in LMWH), the clinical situation (more frequent in postoperative patients than in medical patients and exceptionally in obstetric patients), and the sex (more frequent in women than in men) [4]. HIT occurs in 0.8–3% of all patients treated with UFH for at least 5 days and in less than 1% of patients receiving LMWH. The vast majority of HIT cases are type I and less than 1% are type II HIT with thrombosis.

Not all cases of thrombocytopenia occurring in patients treated with heparin are HIT. For this reason, it is necessary to exclude other unrelated causes of thrombocytopenia such as infections, disseminated intravascular coagulation, human immunodeficiency virus, mechanical devices, hepatic failure, hepato- or splenomegaly, cancer, immune thrombocytopenic purpura, hematological malignancies, bone marrow aplasia, paroxysmal nocturnal hemoglobinuria, pregnancy, massive transfusion, alcoholism, hypothermia, thrombotic thrombocytopenic purpura, vasculitis, systemic lupus erythematosus or pseudo thrombocytopenia. It is especially important to identify possible drugs other than heparins that may cause thrombocytopenia. Non-HIT drug-induced thrombocytopenia [11] can be caused by a hapten-dependent mechanism (such as penicillin and cephalosporins), by drug-dependent antibodies (such as quinidine and non-steroidal anti-inflammatory drugs), by exposure of binding sites induced by ligands recognized by natural antibodies (such as tirofiban and eptifibatide), or by induction of platelet-specific autoantibodies (such as gold salts and procainamide). Drug-induced thrombocytopenia not due to HIT often causes bleeding, but in HIT bleeding is rare even when fully anticoagulated [7].

Clinical Features of HIT

The sudden fall in platelet count associated with heparin treatment is the main diagnostic manifestation of HIT [1–3, 6, 9, 10]. Thrombocytopenia usually occurs 4 to 16 days after heparin exposure. However, thrombocytopenia can occur within hours to 1–2 days if the patient has had recent heparin exposure (within the last 100 days). Exceptionally, HIT may occur days to weeks after discontinuation of heparin (9–30 days) in a delayed onset HIT. Approximately 80% of type II HIT cases have platelet counts between 20 and 150×10^9/L, 10% of cases have platelet counts $<20 \times 10^9$/L with no associated bleeding and 10% of cases never have platelet counts $<150 \times 10^9$/L.

In HIT, thrombocytopenia or platelet count fall has been defined as a platelet count $<150 \times 10^9$/L, or a >50% decrease in platelet count from baseline (although the nadir is still $>150 \times 10^9$/L), or a >30–50% decrease in platelet count from baseline with documented thrombosis. Thus, in HIT it is a criterion for relative thrombocytopenia, rather than absolute thrombocytopenia. In HIT, the platelet count recovers after heparin withdrawal in a median of 4 days. The diagnosis of HIT is unlikely when platelets recover despite continued heparin therapy.

The second defining sign of type II HIT is the occurrence of thrombotic events [1–3, 7, 9, 10, 12]. These thromboses can appear in both the venous and arterial circulation. Venous thromboses account for approximately 70–80% of thrombotic events in HIT, while arterial thromboses account for the remaining 30–20%. In addition, thrombosis in HIT can affect any vascular bed, including both large vessels and microvasculature. The most frequent sites of venous thrombosis in HIT are deep vein thrombosis, pulmonary embolism, cerebral dural sinus thrombosis, and adrenal hemorrhagic infarction. Arterial thromboses are represented by acute thrombotic stroke, myocardial infarction, aortic occlusion, intracardiac thrombosis, and peripheral arterial thrombosis in the extremities, mesenteric or renal. Other atypical clinical manifestations of HIT are (1) heparin-induced skin necrosis, which occurs at the sites of heparin administration and does not present thrombocytopenia in 75% of cases, (2) generalized anaphylactic-type reactions (systemic inflammatory response syndrome), with onset within 5–10 min with a sharp drop in platelets in patients with re-exposure to heparin (<100 days) with fever, chest pain, dyspnea and possible cardio respiratory arrest, and (3) disseminated intravascular coagulation, in 5% of cases. Thrombotic events occur in 40–60% of cases of type II HIT. Thromboses usually occur early and are often severe, with mortality ranging from 10 to 20% and high morbidity, including 5% of cases with amputations.

Thrombocytopenia may precede, coincide with, or follow the thrombotic event. Platelet counts infrequently fall below 10×10^9/L in the absence of extensive thrombosis or comorbidities.

Clinical Diagnosis of HIT

The diagnosis of HIT is based on clinical signs and serological determinations. Serological markers are very useful, but must be interpreted within the clinical context, and are not necessary as part of the diagnostic criteria [4–7].

In the diagnosis of HIT, the first difficulty is to differentiate a thrombocytopenia potentially attributable to heparin from the many other causes and drugs that can lead to low platelet counts. A sharp drop in platelet counts in the presence of concomitant heparin use may lead to clinical suspicion. Although the likelihood of developing HIT increases with increasing dose and duration of heparin therapy, HIT can occur even with low-dose administration for prophylaxis or in heparin-coated catheters or line flushes.

The 4T score [6], named after the initials of the parameters Thrombocytopenia, Timing of onset of platelet fall, Thrombosis, and oTher cause of platelet fall, is used in the diagnosis of HIT. The 4T scoring system is shown in Table 110.2. The sum of the points in the four parameters indicates the clinical probability of HIT. If the 4T score is between 6 and 8 the patient is at high risk of HIT, if the score is between 4 and 5 the risk of HIT is moderate, and if the score is between 0 and 3 the risk of HIT is low. This score is

Table 110.2 The 4T score for pretest probability of heparin-induced thrombocytopenia

	Score
Thrombocytopenia	
• >50% fall and platelet nadir $\geq 20 \times 10^9$/L	2
• 30%–50% fall or platelet nadir $10–19 \times 10^9$/L	1
• <30% fall or platelet nadir $<10 \times 10^9$/L	0
Timing of onset of platelet fall	
• Clear onset 5–10 days, or ≤1 day if previous heparin exposure within the last 30 days	2
• 5–10 days but not clear, or ≤1 day if previous heparin exposure within the last 30–100 days, or onset after day 10	1
• ≤4 days, with no recent heparin exposure	0
Thrombosis or other clinical sequelae	
• New thrombosis, skin necrosis, or acute systemic reaction post intravenous heparin bolus	2
• Progressive or recurrent thrombosis, erythematous skin lesions, suspected but not proven thrombosis	1
• None	0
OTher cause of platelet fall	
• No other explanation	2
• Possible other cause evident	1
• Definite other cause present	0

The sum of the score points indicates the clinical probability of heparin-induced thrombocytopenia

- Score 6 to 8: High probability
- Score 4 to 5: Moderate probability
- Score 0 to 3: Low probability

used to define the probability prior to serological tests and its result helps to indicate the therapeutic approach. A limitation of the 4T score is the difficulty in standardizing whether another cause of thrombocytopenia is "possible" or "definite" and the decision is left to the discretion of the clinician.

HIT is confirmed in 10–20% of cases with a score value of 4–5 points and in 40–80% for scores >6. If the calculated score is ≥4, HIT antibody determination should be performed using the techniques detailed below. For this purpose, whole blood, serum, or plasma samples (depending on the test to be performed) should be drawn at least 4 h after the last administration of heparin.

Laboratory Test for Anti-PF4 Antibodies

It is important to note that not all anti-PF4 IgG antibodies cause HIT. The incidence of PF4–heparin antibodies is much higher than the HIT syndrome itself. Asymptomatic seroconversion is common in patients treated with UFH or LMWH. Anti-PF4/heparin antibodies can be detected in 8–18% of medical or surgical patients treated with UFH and in 2–8% of those treated with LMWH. Anti-PF4 antibodies appear in approximately 50% of patients undergoing cardiac surgery. These anti-PF4 antibodies can be of IgG, IgA, and IgM classes, but the IgG antibodies have the greatest ability to trigger platelet activation. The reason why some patients develop thrombocytopenia and thrombosis while others remain asymptomatic is unknown.

There are several tests to determine the presence of anti-PF4 antibodies [2, 5, 13]. They can be classified into two main groups: functional tests and antigen-based assays. Historically, two functional tests were the only methods available for the demonstration of anti-PF4 antibodies: the platelet aggregation test (heparin-induced platelet activation or HIPA) and the specific granular content release test (serotonin release test or SRA). Although functional tests remain the "gold standard" for clinically relevant anti-PF4 antibodies, these methods are complex and limited to a few specialized laboratories. For these reasons, antigen-based assays have been developed. Some of these antigen-based tests are available on automated analyzers or stand-alone devices that shorten the processing time for a faster result. In general, functional tests are more specific and less sensitive, and are technically more complex and difficult. The antigen-based assays available are the rapid screening tests, the enzyme-linked immunosorbent assays (ELISA), and the chemiluminescence immunoassay (CLIA).

Among the rapid screening tests, which can give results in less than 1 h, there are qualitative and quantitative tests [5]. Qualitative tests include the lateral flow immunoassay (LFIA) and particle gel immuno and immunofiltration assays (PaGIA and PIFA) and the quantitative is the latex immunoassay (LIA IgGAM). LFIA detects anti-PF4 antibodies bound to gold nanoparticles as they move laterally (fluid phase) along a membrane. The IgG complexes are immobilized to generate a visible line. Fresh samples should be used in this assay to avoid interferences. PaGIA uses centrifugal column technology to capture IgG, IgA, and IgM antibodies in PF4-heparin complexes bound to red polystyrene microspheres as they rotate through a column. PIFA is based on the vertical flow of samples in the presence of PF4-coated microspheres through a membrane filter. In the latex immunoassay (LIA IgGAM), the patient's anti-PF4/heparin antibodies compete with latex beads coated with HIT-like antibodies for PF4/polyvinyl sulfonate complexes by inhibiting agglutination. This assay is performed on an automated analyzer with a sensitivity and specificity superior to manual rapid assays.

Enzyme-linked immunosorbent assays (ELISA) for the detection of anti-PF4 antibodies are typical ELISA assays, but some of them include an inhibitory confirmation step with high doses of heparin [2, 5, 13]. There are IgG-specific ELISAs and polyspecific ELISAs, which also detect non-pathogenic IgA and IgM classes. The specificity of IgG-specific ELISAs is higher than that of polyspecific ELISAs. All anti-PF4 ELISA methods have excellent sensitivity. The negative predictive values of IgG-specific and polyspecific ELISAs are both around 0.99, but IgG-specific assays have a higher positive predictive value of 0.56 compared to polyspecific methods where they have a positive predictive value of 0.32. Non-heparin-dependent anti-PF4 antibodies, which can cause vaccine-induced immune thrombotic thrombocytopenia (VITT) can be detected in anti-PF4 ELISAs. A positive anti-PF4 ELISA without functional assays does not fully confirm the presence of HIT, although there is a good correlation between a high positive ELISA result and a positive functional assay.

Chemiluminescence immunoassay (CLIA) is an immunoassay technique where the indicator of the analytic reaction is a luminescent molecule. IgG-specific CLIA methods have a good sensitivity with a lower specificity [5]. As with ELISAs, a positive IgG-specific CLIA without functional assay confirmation does not fully confirm the presence of HIT.

Platelet activation assays measure platelet aggregation or a specific marker of platelet activation. All these assays measure platelet activation in the presence of anti-PF4 antibodies plus heparin. Confirmation of HIT is determined by inhibition of the platelet activation in the presence of a high heparin concentration [2, 5, 13]. All these assays have the major limitation that they require platelets from donors that have been shown to be sensitive to anti-PF4 antibody with added heparin.

Heparin-induced platelet activation assay (HIPA) consists of the visual inspection of platelet aggregation while being stirred in the presence of high and low doses of heparin. HIPA is considered as a "gold standard" method for HIT diagnosis [5].

Light transmission aggregometry (LTA) determines platelet aggregation in platelet-rich plasma by measuring the increase in light transmission in response to the addition of low and high concentration of heparin to a platelet suspension. The increase in light transmission correlates with the formation of platelet aggregates in the presence of low concentration of heparin and its inhibition by higher concentration [5]. LTA can also be performed using adenosine triphosphate (ATP) release as a measure of platelet aggregation. Positive LTA results are defined as >20% aggregation on light transmission or detection of ATP production.

Multiple electrode aggregometry (MEA) is a heparin-induced multielectrode aggregometry that has the same LTA principle but utilizes whole blood. MEA anti-PF4 detection specificity is similar to the specificity of serotonin-release assay [5].

Serotonin-release assay (SRA) is performed by incubating a patient's sample with washed and ^{14}C-radiolabeled donor platelets, which have been determined to be susceptible to platelet activation by HIT antibodies. Upon activation, radiolabeled serotonin is released, and a positive result requires at least 20% (or 50% in other definitions) serotonin release over background reactivity. An additional control can be obtained by adding a monoclonal antibody to block platelet FcγIIa receptors. SRA is the "gold standard" of functional HIT assays for detecting pathogenic antibodies, but this assay has several limitations [5]. The main limitation of this test is that it requires the use of radioisotopes to detect serotonin release, which means that it cannot be performed in more than a few laboratories. Non-radioactive high-performance liquid chromatography may be an alternative. HIPA and SRA have a good correlation for positive HIT patients.

Flow cytometry can also be used as a functional test of HIT [5]. Platelet activation induces extracellular expression of specific antigens such as annexin V and P-selectin (CD62P) that can be detected on platelets by flow cytometry, a multiparametric analysis of single cells in solution. Flow cytometry has good specificity and sensitivity and appears to provide earlier detection of HIT antibodies than SRA.

Overall, laboratory tests for HIT have a high negative predictive value, but only a moderate-low positive predictive value. A positive test is not sufficient for the diagnosis of HIT but increases the probability of HIT. Functional tests (SRA, HIPA) are the most specific. The probability of a diagnosis of HIT increases with a higher 4T score and a stronger positive test result. Also, the risk of thrombosis increases with the intensity of anti-PF4 IgG antibodies and the level of thrombocytopenia.

Routine HIT-IgG screening is not recommended in patients receiving heparin in the absence of thrombocytopenia or thrombosis, while is recommended in patients with decreased platelet counts or thrombosis who are receiving heparin or have received it in the previous 2 weeks or are postoperative cardiac surgery patients with decreased platelet counts or thrombosis between days 5 and 14 [2, 5].

Treatment

If the patient is diagnosed as high risk for HIT (e.g., with a 4T score ≥6), diagnostic testing for anti-PF4 antibodies for HIT should be performed. Pending laboratory results, heparin treatment should be discontinued, further contact with heparin should be avoided, and an alternative anticoagulant therapy to heparin should be initiated immediately [2]. It's necessary to monitor platelet counts recovery. In addition, prophylactic platelet transfusion should be avoided in the absence of hemorrhagic symptoms. In patients with a 4T score of low risk, no changes in treatment are required and anti-PF4 antibody testing is not recommended [2].

Anticoagulant drugs that have been used in HIT as alternatives to UH and LMWH are argatroban, a direct thrombin inhibitor that has an approved indication for the treatment of HIT, danaparoid, an antithrombin-dependent factor Xa inhibitor that has an approved indication for the treatment of HIT in most countries, bivalirudin, a selective direct thrombin inhibitor also approved for the treatment of HIT in some countries, fondaparinux, an indirect thrombin inhibitor, and direct oral anticoagulants such as rivaroxaban, a direct factor Xa inhibitor [1, 5, 8, 11]. Coumarin anticoagulants should be postponed until platelet counts recover (platelet counts above 150×10^9/L) and be initially overlapped with a parenteral anticoagulant.

Anti-PF4 Syndromes

Years after the definition of HIT, several atypical forms, such as late-onset HIT, persistent (refractory) HIT, heparin "flush" HIT and fondaparinux-associated HIT, which did not fit well with the clinical definition of classical HIT, were subsequently identified and classified under the definition of HIT autoimmune disorders [1, 8]. Subsequently, new related syndromes were identified that have in common to be autoimmune entities related to anti-PF4 antibodies with thrombocytopenia and thrombosis. These anti-PF4 antibodies are not always heparin-dependent in all of them, but in some they have heparin-independent antibodies. The emergence of the COVID-19 vaccine-induced immune thrombotic thrombocytopenia syndrome (VITT)) has brought these syndromes to the forefront and has led to the redefini-

Table 110.3 Anti-platelet factor 4 disorders

Anti-PF4 disorder	Anti-PF4 antibodies	Trigger	Thrombosis
Classical HIT	Heparin-dependent	Unfractionated heparin Low molecular weight heparin	30%–70%
Autoimmune HIT	Heparin-dependent heparin-independent	Unfractionated heparin Low molecular weight heparin Fondaparinux	> 95%
Spontaneous HIT	Heparin-independent	Total knee arthroplasty Infection	>95%
VITT	Heparin-independent	Adenovirus vaccine	>95%
Spontaneous VITT	Heparin-independent	Adenovirus infection Chronic autoimmune disorders Monoclonal gammopathy	>95%

HIT heparin-induced thrombocytopenia, *VITT* vaccine-induced immune thrombotic thrombocytopenia

tion of the currently considered anti-PF4 syndromes, which are classical HIT, autoimmune HIT, spontaneous HIT, VITT, and spontaneous VITT [1, 8]. These anti-PF4 syndromes are summarized in Table 110.3.

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Autoimmune Coagulopathies

111

Dolors Tàssies and Joan Carles Reverter

Abstract

Autoimmune coagulopathies (AiC) are rare, acquired bleeding disorders that are characterized by the development of autoantibodies directed to a coagulation factor. These antibodies cause immune-mediated depletion or inhibition of coagulation factors, and consequently, increase the risk of bleeding. AiC have been described in almost all coagulation factors but the most frequently targeted is factor VIII (acquired hemophilia A), followed by von Willebrand factor (vWF) (acquired von Willebrand disease). Clinically, they are characterized by the sudden onset of bleeding episodes in individuals without previous history of bleeding disorder and their treatment consists of control of bleeding with hemostatic therapy, eradication of the inhibitor mainly with immunosuppressive therapy and treatment of the underlying disease if any.

Keywords

Autoimmune coagulopathies · Bleeding disorders · Coagulation factor · Acquired hemophilia A · Acquired von Willebrand disease

Autoimmune coagulopathies (AiC) are rare, acquired bleeding disorders that are characterized by the development of autoantibodies directed to a coagulation factor. These antibodies cause immune-mediated depletion or inhibition of coagulation factors, and consequently, increase the risk of bleeding. AiC have been described in almost all coagulation factors but the most frequently targeted is factor VIII (acquired hemophilia A), followed by von Willebrand factor (vWF) (acquired von Willebrand disease) [1, 2]. Acquired inhibitors against other coagulation factors are far less common [3]. Due to their rarity, AiC are often underdiagnosed.

Clinically, AiC are characterized by the sudden onset of bleeding episodes in individuals without previous history of bleeding disorder. Although infrequent, AiC are potentially life-threatening diseases, so raising awareness about them is necessary to improve early diagnosis and treatment.

The treatment for AiC consists of control of bleeding with hemostatic therapy, eradication of the inhibitor mainly with immunosuppressive therapy, and treatment of the underlying disease if any.

Acquired Hemophilia A

Acquired hemophilia A (AHA) is caused by the development of neutralizing autoantibodies directed against the coagulation factor VIII (FVIII) which leads to a decrease in the FVIII activity. The anti-FVIII autoantibodies are usually polyclonal immunoglobulin G (IgG), mainly IgG4 subclass and rarely IgM or IgA or combinations of them [4].

AHA has an estimated incidence of 1.3–1.5 cases per million persons/year [1]. AHA can affect men and women of all ages although is more frequent in the elderly with a median age at diagnosis of 74 years [5]. However, more than 5% of AHA cases occur in young women in relation to the postpartum period, usually between 1 and 4 months, although cases have been documented up to 1 year after delivery. Less frequently AHA can occur during pregnancy or delivery [6].

More than 50% of AHA cases are idiopathic. The remaining cases are related to autoimmune diseases, cancer, infections, dermatological diseases, drugs, and pregnancy [7] (Table 111.1).

Clinical Manifestations

Soft tissue bleeding (subcutaneous, muscular) is the most frequent symptom of AHA. Subcutaneous bleeding occurs in approximately half of patients [8]. Other common localizations of bleeding are gastrointestinal and retroperitoneal. In

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Table 111.1 Underlying disorders related to acquired hemophilia A and acquired von Willebrand syndrome[a]

	AHA		AvWS	
Disorder	Disease	Frequency	Disease	Frequency
Idiopathic	Unknown	44–67%	Unknown	<5%
Immunological	SLE Rheumatoid arthritis Sjögren syndrome Multiple sclerosis Myasthenia gravis autoimmune thyroid disorders	9–20%	SLE Autoimmune thyroid disorders Connective tissue diseases GvHD	<5%
Hematological malignancy	Multiple myeloma MGUS Waldenström macroglobulinemia Non-Hodgkin lymphoma Chronic lymphocytic leukemia Myelodysplasia myelofibrosis	5–10%	Multiple myeloma MGUS CLL Essential thrombocythemia MGUS Multiple myeloma Waldenstrom macroglobulinemia Chronic lymphocytic leukemia Hairy cell leukemia Lymphomas Essential thrombocythemia Polycythemia vera Chronic myeloid leukemia	48%
Solid malignancy	Prostate Lung Colon Gastric Pancreas Kidney	12%	Wilm's tumor, Lung and bladder adenocarcinoma Urothelial	Rare
Pregnancy	–	2–15%	na	na
Cardiovascular	na	na	Aortic stenosis Congenital heart disease Left ventricular assist devices ECMO-induced	20%
Drug-induced	Beta-lactam antibiotics chloramphenicol Sulfa drugs Phenytoin Methyldopa Interferon-α Fludarabine Clopidogrel NSAIDs Alemtuzumab DPP-4 inhibitors ICI therapy	2–5%	Valproic acid Cephalosporine ICI therapy Antibiotics (griseofulvin, ciprofloxacin), anticonvulsants (valproic acid) Plasma volume expander	Rare
Dermatological	Psoriasis and pemphigus	1–4%	na	na
Infections	HIV Influenza SARS-Cov2	2–4%	Viral infections Parasitical infections	Rare
Other causes	Acute hepatitis B and C chronic obstructive pulmonary disease Asthma	12–17%	Hyperfibrinolysis, uremia, hypothyroidism	<10%

AHA acquired hemophilia A, *AvWS* acquired von Willebrand syndrome, *ICI* immune checkpoint inhibitors, *MGUS* monoclonal gammopathy of unknown significance, *GvHD* graft-versus-host disease, *SLE* systemic lupus erythematosus, *DPP-4* dipeptidyl peptidase 4 inhibitors, *NSAIDs* nonsteroidal anti-inflammatory drugs, *ECMO* extracorporeal membrane oxygenation, *na* not associated

[a] Based on Refs. [1, 19, 20]

postpartum AHA, genital bleeding is the main clinical manifestation. In contrast to patients with congenital hemophilia A, joint bleed is rarely seen in AHA.

Due to the rarity of AHA, it is often difficult to identify it at first glance. A bleeding episode of sudden onset in an individual without previous personal or familiar history of bleeding disorder, mostly in an older subject or a postpartum woman, should raise suspicion of AHA.

Diagnosis

An aPTT (activated partial thromboplastin time) prolongation with normal PT (prothrombin time) in a patient with acute or recent onset of bleeding is very suggestive of AHA. An unexplained isolated prolongation of the aPTT should always be investigated, especially prior to surgery or invasive procedures [8].

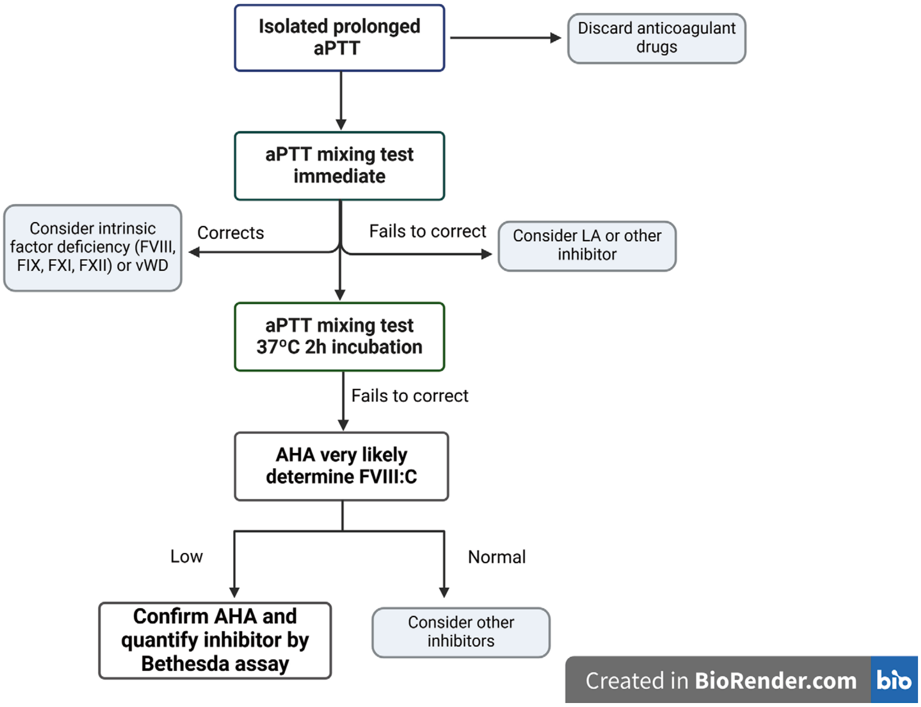
Isolated prolonged aPTT
Discard anticoagulant drugs
aPTT mixing test immediate
Corrects
Consider intrinsic factor deficiency (FVIII, FIX, FXI, FXII) or vWD
Fails to correct
Consider LA or other inhibitor
aPTT mixing test 37°C 2h incubation
Fails to correct
AHA very likely determine FVIII:C
Low
Normal
Confirm AHA and quantify inhibitor by Bethesda assay
Consider other inhibitors
Created in BioRender.com bio

Fig. 111.1 Diagnostic flowchart of acquired hemophilia A

Laboratory diagnosis should be made by a stepwise approach. An algorithm for laboratory diagnosis of AHA is shown in Fig. 111.1.

Mixing studies consistent in the mix in 1:1 volume of patient and normal plasma may help to differentiate factor deficiency from the presence of an inhibitor. Testing of aPTT in the mixing studies is recommended to be done both immediately and after incubation at 37 °C for 2 h because inhibitors in acquired hemophilia A are time- and temperature-dependent [9].

In the immediate mix test, correction of aPTT is suggestive of coagulation factor deficiency, while a prolongation here is suggestive of lupus anticoagulant (LA) or heparin.

In the mix test after incubation at 37 °C for 2 h, a prolonged aPTT is suggestive of inhibitors as AHA and next, levels of intrinsic coagulation pathway factors should be measured [8]. Over 90% of acquired inhibitors are caused by antibodies against FVIII. In AHA, coagulation factor dosing will demonstrate a reduction in factor VIII activity.

AHA is confirmed by quantifying the FVIII inhibitor titer in the Bethesda assay, Nijmegen Bethesda assay, or in some laboratories by an enzyme-linked immunosorbent assay (ELISA) anti-FVIII antibody [8].

The Bethesda assay is usually used in patients with congenital hemophilia A to quantify FVIII alloantibodies, that display linear type 1 kinetics. However, in AHA the autoantibodies usually display complex and non-linear type 2 kinetics and consequently, the Bethesda assay, although useful in detecting factor VIII inhibitors in AHA, may not be able to estimate the true potency of the autoantibody [10].

The inhibitor titer is equal to the reciprocal of the plasma dilution that results in 50% inhibition of FVIII in normal plasma after incubation for 2 h at 37 °C [11]. Inhibitor titers are measured in Bethesda units (BU) where 1 BU is equal to the amount of antibody that neutralizes 50% FVIII activity. The Nijmegen modification has been developed to improve the detection of low-titer inhibitors [12]. Pre-analytical heat inactivation at 56 °C of the patient's plasma to precipitate circulating residual FVIII, prior to assessment of the test, may improve assay sensitivity and specificity.

Testing for anti-porcine inhibitors using a modified Bethesda assay is recommended if treatment with recombinant porcine factor VIII (rpFVIII) is an option [8]. The assay is performed in the same way as the Bethesda assay, but with rpFVIII as the substrate instead of normal human plasma.

Anti-factor VIII antibodies ELISA are sensitive and specific for detecting FVIII antibodies but are not able to distinguish neutralizing capacity [8]. ELISA may be helpful in demonstration of anti-FVIII autoantibodies when interference with LA is suspected in a positive Bethesda assay.

Potential Difficulties in the Laboratory Diagnosis of AHA

As previously mentioned, in AHA there is a lack of correlation between FVIII residual levels or inhibitor titer in the Bethesda assay and bleeding phenotype, due to the nonlinear kinetics of inactivation of FVIII of inhibitors. Then, the Bethesda assay may underestimate the inhibitor titer.

LA should be excluded as a potential cause of isolated prolonged aPTT. AHA inhibitors and LA are sometimes difficult to differentiate. Moreover, both are autoimmune disorders that can occur simultaneously in patients [13]. Although AHA autoantibodies and LA are acquired autoimmune coagulation inhibitors, they exhibit different pathophysiologic mechanisms and clinical manifestations.

In studies of aPTT mixing LA will usually show an immediate inhibitory effect in the mixing study, while AHA inhibitors could initially correct the aPTT prolongation but show their inhibitory effect after incubation 2 h at 37 °C.

As LA can prolong the aPTT to a variable extent, it can interfere with aPTT-based factor assays, including FVIII. Interference of LA on FVIII activity can be excluded by using chromogenic substrate FVIII assays that are usually insensitive to LA [8, 13].

Immunoassays to detect anti-FVIII antibodies may help to distinguish LA from FVIII inhibitors. LA can also be excluded through a negative diluted Russel viper venom time (dRVVT), that is insensitive to FVIII inhibitors [14].

Therapeutic anticoagulants, such as heparins and direct anticoagulants, may prolong aPTT and resemble circulating inhibitors in laboratory tests. To detect anticoagulants that inhibit activated factor X (heparin, low-molecular-weight heparins, fondaparinux, danaparoid, and direct oral factor Xa inhibitors), an anti-Xa assay is helpful. Otherwise, thrombin clotting time, with or without reptilase time, may be helpful in distinguishing the effects of heparin and direct thrombin inhibitors (lepirudin, argatroban, and dabigatran) from AHA [14].

Acquired von Willebrand syndrome is usually easy to differentiate from AHA, because the aPTT mixing study and the Bethesda assay will be negative.

Treatment

The treatment of AHA is based on control of acute bleeding with hemostatic therapy and eradication of the inhibitor mainly with immunosuppressive therapy. Patients with AHA should be referred to expert centers [15].

Hemostatic treatment must be initiated in patients with clinically relevant bleeding, irrespective of residual FVIII activity and inhibitor titer [8]. Bypassing agents such as recombinant activated factor VII (rFVIIa), activated prothrombin complex concentrate (aPCC) or rpFVIII are considered first-line treatments for clinically relevant bleeding in patients with AHA and are recommended over other less effective therapies such as human FVIII concentrates or desmopressin [5, 8].

It must be considered that any hemostatic treatment is associated with a potential risk of thrombotic events, particularly in patients with cardiovascular risk factors.

Recently, emicizumab has been tested in AHA patients. Emicizumab is a bispecific antibody that mimics the cofactor function of activated FVIII and is not affected by FVIII inhibitors. Emicizumab is used to prevent bleeds in patients with congenital hemophilia A both with and without inhibitors [16]. A recent prospective, multicenter, open-label phase III study of emicizumab prophylaxis in patients with acquired hemophilia A suggests that emicizumab prophylaxis may have a favorable benefit-risk profile in AHA [17].

Immunosuppressive therapy should be started immediately after diagnosis to eradicate autoantibodies and induce remission of AHA. Regimens include corticosteroids (e.g., prednisone or prednisolone 1 mg/kg body weight), rituximab (e.g., 375 mg/m^2 body surface area once weekly for 4 weeks), and/or cyclophosphamide (1–2 mg/kg body weight daily for a maximum of 6 weeks) [15]. Caution should be taken with older patients due to high infection risk related to immunosuppressants.

Although not considered today's first-line therapy, plasma exchange is an effective method to quickly remove the circulating factor VIII inhibitor and alleviating AHA severity [18].

Treatment of the underlying cause (i.e., cancer, infection, autoimmunity) or stopping a drug associated with AHA, may improve the course of the disease and reduce the risk of recurrence.

Acquired von Willebrand Syndrome

Acquired von Willebrand syndrome (AvWS) is often unrecognized or misdiagnosed as congenital von Willebrand disease (vWD). Contrary to inherited vWD, AvWS occurs in persons without previous personal or family history of bleeding and almost always occurs in association with an underlying disorder, most frequently lymphoproliferative, myeloproliferative, and cardiovascular diseases [19] (Table 111.1).

The pathophysiology of AvWS includes several mechanisms such as specific antibodies that cause functional interference or nonspecific antibodies that form circulating immune complexes and lead to increased clearance of vWF, adsorption to surfaces of malignant cells and enhanced shear stress resulting in proteolysis of vWF by ADAMTS13 [19, 20].

The bleeding spectrum in AvWS ranges from mucosal bleeding, cutaneous hematomas, hematuria, and gastrointestinal bleeding, to joint and muscle bleeds [19, 20].

Table 111.2 Laboratory differential diagnostic between Factor VIII inhibitor and lupus anticoagulant

	Factor VIII inhibitor	LA
aPTT	Prolonged	Prolonged
FVIII activity (aPTT-based assay)	Low	Sometimes artificially reduced
FVIII activity (chromogenic assay)	Low	Normal
Anti-FVIII antibody-ELISA	Present	Absent

LA lupus anticoagulant, *FVIII* factor VIII, *aPTT* activated partial thromboplastin time, *ELISA* enzyme-linked immunosorbent assay
Modified from Ref. [4]

Diagnosis

Laboratory findings resemble those found in inherited vWD. A defect in primary hemostasis is demonstrated by a prolonged closure time in the platelet function analyzer (PFA) 100 or 200. Factor VIII:C activity is reduced in most AvWS patients, and then a prolonged aPTT can be observed, but in contrast to AHA, a 1:1 mixing test with normal plasma shows here a normalization of the aPTT because no inhibitor against FVIII is present in AvWS. Usually a mild decrease in vWF:Ag is seen, with a more marked decrease in functional VWF activity (VWF:Ac) [20]. Accordingly, vWF:Ac/vWF:Ag ratios are often below 0.7, similar to type 2 vWD. The loss of high-molecular-weight multimers is demonstrated by vWF multimer electrophoresis (Table 111.2).

In contrast to AHA, inhibitory autoantibodies in AvWS are rarely demonstrated.

The mixing test (1:1 volume patient plasma mixed with normal plasma and incubated at 37 °C for 2 h, followed by the measurement of residual vWF) is used to look for an inhibitory activity against vWF. However, the non-neutralizing antibodies that bind vWF and accelerate its plasma clearance cannot be detected with this method [19, 20].

The differential diagnosis must be done with congenital vWD, and other autoimmune acquired coagulopathies (i.e., AHA).

Treatment of AvWS is based on the control of acute bleeding, its prevention in surgery or invasive procedures, and the treatment of the underlying medical condition [21].

Hemostatic therapies include desmopressin (DDAVP), vWF/FVIII concentrates, antifibrinolytic agents, high-dose intravenous immunoglobulins, plasmapheresis, and recombinant activated factor VII (rFVIIa) [19–21].

Other Autoimmune Coagulopathies

There are descriptions of acquired inhibitors of fibrinogen (factor I), factor II, V, VII, IX, X, XI, XII, and XIII either in children or in adults with or without associated disorders [2]. Among them, autoimmune factor V and factor XIII deficiencies are the most frequent.

Autoimmune Factor V Deficiency

Neutralizing autoantibodies to FV usually occur in elderly people and in association with topical bovine thrombin exposition, surgery, antibiotic therapy (β-lactam group, aminoglycoside), or malignancy [3].

Bleeding manifestations are like those of congenital FV deficiency and range from mild mucosal bleeding to life-threatening hemorrhage (retroperitoneal, gastrointestinal). An inhibitor to FV should be suspected when a prolonged aPTT and PT do not correct with mixing studies and FV activity is low. The titer of the antibody can be estimated with a modified Bethesda assay [3, 10].

Bleeding episodes can often be managed with fresh frozen plasma (FFP) and platelet transfusions because platelet FV can bypass some inhibitors. For unresponsive bleeds, bypassing agents such as aPCC and rFVIIa have been used [3].

Inhibitor eradication therapy includes immunosuppression, plasma exchange, rituximab, or high-dose intravenous immunoglobulins. Because autoimmune FV inhibitors may disappear spontaneously over weeks to months, it is uncertain whether immunosuppressive therapy affects the inhibitor's natural history [2].

Autoimmune FXIII Deficiency

Autoimmune FXIII deficiency is due to the development of neutralizing or non-neutralizing antibodies against the subunit A or the subunit B of FXIII [3]. Autoimmune FXIII deficiency usually affects elderly people and has been associated with autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis), malignant diseases (monoclonal gammapathies), and drugs (isoniazid, penicillin, phenytoin, amiodarone) [2, 3].

Bleeding manifestations may be more severe that congenital FXIII deficiency and include intramuscular and subcutaneous bleeding, hemarthroses, and bleeding in critical sites such as intracranial and retroperitoneal bleeding [10, 22].

Screening coagulation tests, such as the aPTT, PT, TT (thrombin time), and fibrinogen level, are usually normal. Plasma FXIII activity is diminished. Mixing tests can help in the diagnosis, but it is necessary to perform immunological tests to measure FXIII inhibitors to make a definitive diagnosis [23].

Hemostatic treatment consists mainly in FXIII concentrate or FFP administration. In patients with abnormal bleeding, immunosuppression should be started as soon as the diagnosis is made [2].

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Index

A

- Acetylcholine receptor (AChR), 567
- Achlorhydria, 454
- Acitretin, 513
- ACTTION-APS Pain Taxonomy (AAPT) Criteria, 314
- Acquired ADAMTS13 deficiency, 737
- Acquired hemophilia A (AHA), 747
  - clinical manifestations, 747, 748
  - diagnosis, 748, 749
  - idiopathic, 747
  - incidence, 747
  - potential difficulties in the laboratory diagnosis of, 750
  - treatment, 750
- Acquired von Willebrand syndrome (AvWS), 750, 751
- Acrocyanosis, 700
- Activated partial thromboplastin time (aPTT), 748, 750
- Activated prothrombin complex concentrate (aPCC), 750
- Acute cerebellitis, 619
- Acute cutaneous lupus erythematosus (ACLE), 482, 484
- Acute disseminated encephalomyelitis (ADEM), 607
- Acute febrile pleomorphic anemia with hyaline thrombi, 735
- Acute generalized paralysis, 578
- Acute hematuria, 657
- Acute inflammatory demyelinating neuropathy (AIDP), 578, 579, 581
- Acute interstitial pneumonia (AIP), 542
- Acute kidney injury (AKI), 656, 670, 674
- Acute motor axonal neuropathy (AMAN), 578, 579, 581
- Acute motor sensory axonal neuropathy (AMSAN), 578, 579
- Acute orchitis, 413, 415, 416
- Acute phase reactants, 21
- Acute posterior multifocal placoid pigment epitheliopathy (APMPPE), 645
- Acute rheumatic fever (ARF), 532, 593
- Acute tubulointerstitial nephritis (ATIN), 687
  - causes of, 687, 688
  - diagnostic criteria, 689
  - follow-up, 689
  - immune and systemic diseases, 687
  - laboratory findings, 688
  - pathogenic mechanisms, 687
  - signs and symptoms, 688
  - treatment, 689
- Acute zonal occult outer retinopathy (AZOOR), 637
- Adalimumab, 513, 642, 647
- ADAMTS13 deficiency, 735
- Adaptive immunity, 496, 535, 670
- Addison's disease (AD), 375, 376, 387, 396, 397, 408, 707
  - autoantibodies for, 396, 408
- Adrenal autoantibodies (ACA), 377
- Adrenal insufficiency, 377
- Adrenocorticotropic hormone (ACTH) deficiency, 382, 384, 385
- Adult-onset Still's disease (AOSD), 31, 303
- Alarcón-Segovia's criteria, 57
- Alkaline phosphatase (ALP), 434
- Allogeneic transplant, 714
- Alopecia areata (AA)
  - causes of, 505
  - clinical presentation, 505, 506
  - definition of, 505
  - diagnosis, 506
    - histological examination, 507
    - trichoscopy, 506, 507
  - treatment, 507
- α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), 573, 606
- α-enolase, 384
- Ambrisentan, 554
- American Association of Gynecological Laparoscopists (AAGL) classification, 401
- Amphiphysin-antibodies, 630
- Amyloid angiopathy-Aβ-related angiitis (ABRA), 590
- Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION), 314
- Androgens, 714
- Anemia, 454
- Anifrolumab, 8, 486
- Ankylosing spondylitis (AS), 287, 288, 640
- Anterior uveitis (AU), 639
  - clinical course, 640
  - local treatment for, 640
- Anti-PF4 syndromes, 745, 746
- Anti-ADAMTS13 autoantibodies, 735
- Antiadrenal antibodies, 377
- Anti-β2GPI antibodies, 536
- Antibodies against *Saccharomyces cerevisiae* (ASCAs), 467
- Antibody-mediated autoimmune encephalitis, 604
- Antibody-mediated PRCA, 718
- Antibody-negative autoimmune encephalitis (ANAE), 607, 608
- Anti-calcium-sensing-receptors, 396
- Anti-cardiolipin (aCL) antibody, 11, 590, 600
- Anti-CD40 antibodies, 676
- Anticholinesterase drugs, 569
- Anti-citrullinated antibodies (ACPA), 21
- Anticoagulant, 745
- Anti-contactin-associated protein-like 2 CASPR-2 antibodies, 612
- Anti-DNA, 409
- Anti-dsDNA antibodies, 484
- Anti-endothelial antibodies (AEAs), 599
- Anti-flagellin (CByr1), 467
- Anti-FVIII autoantibodies, 747
- Anti-GAD antibodies, 630
- Anti-GAD ataxia, 618
- Anti-GAD65 (glutamic acid decarboxylase 65), 396
- Antigen-based assays, 744
- Antigen-presenting cells, defects in, 728, 729
- Anti-heart autoantibodies, 527

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Anti-HMGCR antibody, 255
Anti-hsp70 antibodies, 600
Anti-IA2 (tyrosine phosphatase-like protein IA2), 396
Anti-IgLON5 disease, 625–627
Anti-LGI1 encephalitis (LGI1e), 624
Anti-liver-kidney-microsomal antibodies (anti-LKM), 421
Anti-Ma2, 623, 624
Antimitochondrial antibodies (AMA), 262
Anti-nephrin antibodies, 676
Antineutrophil cytoplasmic antibodies (ANCA), 123, 131, 190, 467, 599
Anti-NMDA receptor encephalitis (NMDARe), 606, 624
Antinuclear antibodies (ANA), 3, 26, 399, 404, 409, 435, 483, 599, 683
Antinuclear autoantibodies (ANAs), 77, 650
Anti-PF4 antibodies, 744, 745
Anti-PF4 syndromes, 741
Antiphospholipid antibodies (aPL), 5, 600
Antiphospholipid syndrome (APS), 11, 76, 535, 590, 593, 600, 601
  clinical manifestation, 13
  diagnosis, 14, 15
  epidemiology, 12
  etiology, 12
  history, 12
  laboratory abnormalities, 13
  pathogenic mechanisms, 13
  pathophysiology, 12
  risk stratification, 17
  therapy and prevention, 16
  treatment, 17
Anti-PIT1 hypophysitis, 385
Anti-pituitary-specific transcription factor-1 hypophysitis, 382
Antiplatelet and anticoagulant therapy, 596
Antireceptor antibodies, 409
Anti-rheumatic agents, 539
Anti-*Saccharomyces cerevisiae* antibody (ASCA), 460
Anti-smooth muscle (ASMA) antibodies, 421
Anti-soluble liver antigen (anti-SLA) antibodies, 421
Antisperm antibodies (ASA), 413, 414, 416
Anti-SRP antibody, 255
Antistreptolysin O (ASLO) titer, 593, 595
Antisynthetase antibodies (ASA), 247, 249
Antisynthetase syndrome (ASS), 247, 250, 542
  arthritis, 248
  clinical manifestations, 248
  diagnostic criteria, 251, 252
  epidemiology, 247, 248
  histology, 250, 251
  interstitial lung disease, 248
  myositis, 248
  pathogenesis, 250
  serological features, 251
  symptoms, 252
  therapy, 252, 253
Antithrombotic effects, 600
Antithymocyte globulin (ATG), 714
Antithyroid antibodies, 348
Anti-U1-ribonucleoprotein (anti-U1-RNP)
  antibodies, 56
  autoantibodies, 55, 399
Anti-zona pellucida antibodies, 409
Aplastic anemia (AA), 711
  classification, 712
  clinical manifestations, 712, 713
  diagnosis, 713
  epidemiology, 712
  pathophysiology, 712
  presenting symptoms, 713
  with severity criteria, 713
  treatment
    androgens, 714
    HSCT, 714
    immunosuppressive therapy, 713, 714
    supportive care, 713
Aquaporin-4 (AQP4-IgG), 560, 583
Arginine infusion test, 382
Arterial spin labeling (ASL), 590
Arthritis, 248, 330, 332
Arthritis mutilans, 502
Asbury and Cornblath's clinical criteria, 580
ASMAN, 581
Asymptomatic atrophic autoimmune thyroiditis, 348
Asymptomatic hematuria, 656
Asymptomatic seroconversion, 744
Asymptomatic urinary testing, 656
Atherosclerosis (AS), 670
  diagnosis, 537, 538
    biomarkers, 538
    instrumental tools, 538
  pathogenesis, 535–537
  prevalence, 537
  therapy, 538, 539
Atrial fibrillation, 528
Atrial septostomy, 554
Atrophic autoimmune thyroiditis (AAT), 346
  clinical manifestations, 348
  diagnostic criteria, 349
  diagnostic studies, 349
  differential diagnosis, 348
  epidemiology, 346
  genetic factors, 347
  history, 346
  immunological factors, 347, 348
  pathogenesis, 346, 347
  pathogenic mechanisms, 347
  pathological features, 349
  treatment, 349
Attention deficit hyperactivity disorder (ADHD), 594
ATX-GD-59, 359
Atypical hemolytic uremic syndrome (aHUS), 691, 692
  acquired forms of, 694
  clinical findings, 692
  diagnostic criteria, 693, 694
  hereditary, 694
  laboratory findings and serological markers, 692
  therapy and prevention, 694
Audiovestibular manifestations, 184
Autoantibodies, 21, 37, 39, 42, 50, 384, 389, 396, 423
Autoantibodies against other endocrine systems, 408
Autoantibodies against parathyroids (PTAbs), 389
Autoimmune Addison's disease (AAD), 375, 388
  autoantibodies, 377
  clinical manifestations, 376
  diagnostic criteria, 377
  differential diagnosis, 377, 378
  history and epidemiology, 375
  laboratory features, 376
  pathogenesis, 376
  pathological features, 376
  prognosis, 378
  treatment, 378
Autoimmune adrenal insufficiency, 377

Autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA) syndrome, 323
  adjuvant, 323, 324
  autoimmunity, 324
  clinical manifestations, 324
  clinical spectrum, 324
  diagnostic criteria, 324, 325
  histopathology, 325
  laboratory markers, 324
  neurological symptoms, 325
  pathogenesis, 324
  population at risk, 326
  prevention, 326
  silicone exposition, 323
  symptoms, 325
  therapy, 326
  vaccines, 323
Autoimmune autonomic ganglionopathy (AAG), 611, 612
Autoimmune bullous diseases, 492
Autoimmune cerebellar ataxias (ACA), 615
  clinical features of, 616
  diagnostic criteria, 616
  non-paraneoplastic ACA associated with neuronal antibodies
    and infrequent neuronal antibodies, 618, 619
    cerebellar ataxia and GAD antibodies, 618
  not associated with neuronal antibodies
    gluten ataxia, 619
    postinfectious cerebellar ataxia, 619
  treatment, 619, 620
Autoimmune coagulopathies (AiC), 747
Autoimmune DCM (ADCM), 525, 527, 528
Autoimmune diabetes, *see* Type 1 diabetes
Autoimmune diseases (ADs), 81
Autoimmune disorder, 173
Autoimmune dysautonomia, 611
  AAG, 611, 612
  autoimmune encephalitis, 612
  immune-mediated autonomic and sensory neuropathy, 612
  paraneoplastic autonomic syndromes, 612
Autoimmune encephalitides (AE), 603
Autoimmune encephalitis (AE), 612
  clinical manifestations, 604
    acute disseminated encephalomyelitis, 607
    ANAE, 607
    anti-NMDAR encephalitis, 606
    limbic encephalitis, 606, 607
  diagnosis, 608
  management and prognosis, 608, 609
  neural antibodies, 605–608
Autoimmune epithelitis, 47
Autoimmune factor V deficiency, 751
Autoimmune FXIII deficiency, 751, 752
Autoimmune gastritis (AIG), 451
  autoimmune conditions, 451
  clinical manifestations, 452
  diagnostic criteria, 455, 456
  endoscopic findings, 454, 455
  histological findings, 455
  laboratory findings, 454
  physiopathology, 451
  risk of gastric cancer, 453
  treatment and surveillance, 456
Autoimmune Hashimoto's thyroiditis, 339
  biochemical examinations, 342
  clinical presentation, 340–342
  diagnosis, 342
  drugs, 341
  environmental factors, 341
  estrogens, 341
  etiology, 340
  factors, 341
  genetic factors, 340, 341
  goiter, 339
  highly active antiretroviral therapy, 341
  immune check point inhibitors, 341
  incidence, 340
  laboratory findings, 342
  pathogenesis, 340
  postpartum thyroiditis, 343
  prevalence, 340
  progression, 340
  selenium deficiency, 341
  silent thyroiditis, 343
  subclinical hypothyroidism, 339
  symptoms and signs, 342
  thyroid peroxidase antibodies, 342
  thyroxine, 339
  treatment, 343
  ultrasonography, 342
Autoimmune hemolytic anemia (AIHA), 699
  classification, 699, 700
  clinical findings, 700
  current and emerging therapeutic strategies for, 703
  DAT
    negative, 701, 702
    positivity for IgG, 701
    positivity only for complement, 701
    sensitivity, specificity, and predictive value of, 702
  diagnostic criteria for, 702
  direct antiglobulin test, 701
  hemolysis markers, 700
  immunohematological diagnosis, 701
  markers of hemolysis, 700
  secondary, 702
Autoimmune hepatitis (AIH), 429, 433, 436
  autoantibodies, 423
  clinical presentation, 422
  definition of, 421
  diagnostic criteria, 422
  epidemiology, 421
  histology, 423, 424
  incidence, 421
  revised scoring system, 422
  simplified scoring system, 423
  strategies for the management, 425
  therapy, 424
Autoimmune hypophysitis (AH), 381
Autoimmune lymphoproliferative syndrome (ALPS), 723
Autoimmune metaplastic atrophic gastritis (AMAG), *see* Autoimmune gastritis (AIG)
Autoimmune neutropenia (AINs)
  clinical course of, 724
  clinical features, 724
  diagnosis, 724
  hematological features, 725
  hematological findings, 724
  pathogenesis, 724
  primary, 723
  secondary, 723
  serological tests, 725
  therapy, 725
Autoimmune oophoritis, 408

Autoimmune orchitis, 413
  diagnostic criteria of, 415
  laboratory and imaging, 414
  pathogenesis of, 415
  serological markers of, 414, 415
  signs and symptoms, 413, 414
  therapy and prevention, 416
Autoimmune pancreatitis (AIP), 441
  definition, 441
  diagnosis
    clinical manifestations, 442
    histology, 443
    other organ involvement, 443
    radiological imaging, 443
    serology, 443
  diagnostic criteria, 443–445
  differential diagnosis, 445, 446
  prevalence, 441
  treatment, 446
  type 1, 441, 442
  type 2, 441, 442
Autoimmune podocytopathy, 663
Autoimmune polyendocrine syndromes (APSs), 395
  APS-1, 396
    clinical features, 396, 397
    diagnosis, 397
    pathogenesis, 396
  APS-2, 397
    clinical features, 397, 398
    diagnosis, 398
    pathogenesis, 397, 398
  APS-3, 399
    clinical features, 398, 399
    definition of, 398
    diagnosis, 399
  APS-4, 399
  classification, 396
  therapy for, 399
Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), 388, 396
Autoimmune polyglandular syndrome (APS), 395, 408
Autoimmune regulator (AIRE), 396
Autoimmune retinopathies (ARs)
  antigen proteins, 637
  clinical manifestation, 636
  diagnosis, 636, 637
  differential diagnosis, 637
  epidemiology, 635
  pathologic features, 635, 636
  symptoms and signs, 636
  therapy, 637
Autoimmune rheumatic diseases (AIRD), 535, 538
Autoimmune sensorineural hearing loss (ASNHL), 597
  and APS, 600, 601
  autoantibodies in, 599
  diagnostic criteria, 601
  humoral (autoantibody) response in, 599, 600
  T-cell-mediated autoimmunity in, 598
  treatment, 601
Autoimmune tautology, 85
Autoimmune thyroid disease (AITD), 82
Autoimmune thyroiditis, 395
Autoimmunity, 529
Autoinflammatory diseases (AID), 295
Autonomic disorders, 611
Autonomic nervous system (ANS), 611
Autopsy, 619
Autoreactive T cells, 599
Axial spondyloarthritis (SpA), 291
Axonal degeneration, 707
Azathioprine (AZA), 424, 570, 591, 646

B

B2GPI, 536
Baclofen, 631
Bacterial colitis, 460
Baricitinib, 486, 507
Barkhof–Tintoré MRI criteria, 562
B-cells, 369
Behçet's disease (BD), 161–163
  clinical manifestations, 162
  diagnostic criteria, 163
  history, 162
  prognosis, 163
  serological features, 162
  symptoms, 162
  therapy, 164
Behçet uveitis, 641
Belimumab, 8, 486
Benzodiazepines, 631
Bethesda assay, 749, 750
Bethesda units (BU), 749
Bezafibrate, 431
Bilateral diffuse uveal melanocytic proliferation (BDMUP), 635, 637
Bilateral lung transplantation, 554
Bimekizumab, 513
Biomarkers, 92, 510, 543, 544, 658, 659, 675, 694
Blood pressure (BP)
  diagnostic criteria, 492
  immunoserological hallmark of, 492
  pathological features, 491
  prognosis, 492
  treatment, 492, 493
Blood transfusions, 713
Bone marrow biopsy, 713
Bone marrow failure, 711
Bone marrow transplant, 714
Bosentan, 554
Breast, focal single-organ vasculitis, 215–216
British Isles Lupus Assessment Group (BILAG), 8, 485
Bronchoalveolar lavage (BAL), 544
Bronchoscopy, 544, 545
Budesonide, 424
Buerger's disease, 155, 156, 158
  diagnostic criteria, 157, 158
  serological markers, 156, 157
  signs and symptoms, 156
  treatment, 158, 159
Bulbar muscles, 568
Bullous pemphigoid (BP)
  clinical manifestations, 491
  Cutaneous findings, 491
  definition, 489
  epidemiology, 489
  pathogenesis, 490
Burst-forming unit erythroid (BFU-E), 718

C

C reactive protein (CRP), 538, 650
C3 nephritic factor (C3NeF), 682

Calcineurin inhibitors (CNI), 666, 675
Calcium channel blocker (CCB), 59, 71
Calcium concertation, 390
Cancer antigen (CA)-125, 404
Cancer-associated cone dysfunction, 637
Cancer-associated retinopathy (CAR), 635–637
Caplacizumab, 739
Carbon monoxide diffusing capacity (DLCO), 551
Cardiac index, 552
Cardiac sarcoidosis, 284
Cardiopulmonary exercise testing, 552
Cardiovascular risk (CVR), 535
Carmustine, 637
Carotid intima-media thickness (IMT) measurement, 538
Carpet tack sign, 483
Cast-off skin appearance (CSA), 455
Cataplexy, 623
Catassi and Fasano diagnostic criteria for CD, 476
CD16, 725
CD32, 725
CD4þ T cells, 598
Celiac disease (CD), 471, 619, 706
    clinical manifestations of, 472–473
    criticism on diagnostic criteria, 476
        interferon (IFN)-c-secreting T cells, 477
        intraepithelial lymphocytes with T-cell receptor, 477
        serum IL-2, IL-8, and IL-10, Increased level of, 477
        specific lymphocytes in peripheral blood, Detection of, 477
        subepithelial deposits of IgA antitransglutaminase tissue, 477
    diagnostic criteria, 476
    genetical markers, 475
    histologic markers, 476
    laboratory findings, 473
    prediction, 477
    prevalence of, 471
    risk groups, 473
    serological markers, 474
    signs and symptoms of, 472–473
    therapy and prevention, 477, 478
Cell cholesterol efflux capacity (CEC), 538
Cell-mediated immunity, 390
Cell-surface or synaptic antigens, 604
Central nervous system vasculitis (CNSV), 587
    biopsy findings -histology, 588, 589
    characteristics, 589
    clinical manifestations, 588
    CSF analysis, 588
    diagnosis, 590, 591
    dilemma, 591
    laboratory test, 590
    neuroimaging, 588
    PCNSV, 587, 590
    prognosis, 591
    radiological diagnostics, 587
    SCNSV, 587, 589, 590
    treatment, 591
Cerebellar ataxia, 615
Cerebral amyloid angiopathy-related inflammation (CAA-RI), 590
Cerebral angiography, 587
ChAdOx1-S vaccination, 579
Chapel Hill Consensus Conference (CHCC), 136
Characteristic organ involvement, 59
Chemiluminescence immunoassay (ChLIA), 175, 744
Chilblain LE (CHLE), 483
Chloroquine, 486
Cholangiocarcinoma (CCA), 438
Cholesterol loading capacity (CLC), 538
Chorea minor, 593
Chronic atrophic gastritis (CAG), 705, 708
Chronic bilateral iridocyclitis, 641
Chronic cutaneous lupus erythematosus (CCLE), 482
Chronic demyelinating polyneuropathy (CIDP), 578, 579, 582
Chronic disease, 376
Chronic hypersensitivity pneumonitis (HP), 541
Chronic hypoparathyroidism (CHP), 396, 399
    animal models and cell-mediated immunity, 390
    autoantibodies, 389
    cause of, 387
    classification, 388, 390
    definition of, 387
    diagnosis and clinical manifestations, 390, 391
    epidemiology, 388
    genetics, 389
    history, 387, 388
    idiopathic, 387
    physiology, 390
    therapy, 391
Chronic immune thrombocytopenia, 729
Chronic kidney disease (CKD), 656, 664, 673, 675, 689
Chronic mucocutaneous candidiasis (CMC), 387, 399
Chronic nephritis, 681
Chronic orchitis, 413
Chronic posterior uveitis, 640
Chronic thromboembolic pulmonary hypertension (CTEPH), 549
Chronic tubulointerstitial nephritis, 688
Chronic widespread pain (CWP), 309, 314
Classic Mikulicz syndrome, 318
Classification criteria, 56–58
    Alarcón-Segovia's criteria, 57
    critical analysis of, 58, 59
    definition of, 56
    Kahn's criteria, 57
    Kasukawa's criteria, 57
    Sharp's criteria, 56
    Tanaka's criteria, 58
Classification of psoriatic arthritis (CASPAR) study group, 502
Clinical shift, 55
Clinically definite, 562
Clinically isolated syndromes (CISs), 563
Clobetasol, 499
Cobalamin, 706
    deficiency, 708
Coeliac trait, 477
Coelomic metaplasia theory, 402
Cogan's syndrome, 183
    clinical features, 184
    diagnosis, 185, 186
    ocular manifestations, 184
    ophthalmic manifestations, 184
    pathogenesis, 183, 184
    radiological data, 185
    systemic manifestations, 185
    treatment, 185
Cold agglutinin diseases (CAD), 699, 700, 703
Cold agglutinin syndrome (CAS), 699
Colon cancer prevention, 438
Colonoscopy, 460
Colony-forming unit erythroid (CFU-E), 718
Colorectal cancer (CRC), 461
Complete biochemical response (CBR), 424
Complete remission (CR), 664
Computed tomography (CT), 304, 305

Congenital FV deficiency, 751
Connective tissue diseases (CTDs), 541
Conventional immunosuppressants, 641
Coombs test, 701, 734
Corazza classification, 476
Coronary artery calcium score, 538
Corpus callosum, 168
Correa cascade of gastric carcinogenesis, 453
Corticosteroid, 424
Corticosteroid-dependent nephrotic syndrome (CDNS), 676
Corticosteroid-resistant nephrotic syndrome (CRNS), 674
Corticosteroids, 424, 486, 601, 637, 641, 677, 720
Corticosteroids-sensitive nephrotic syndrome (CSNS), 676
COVID-19, 516, 579, 718
COVID-19 vaccine-induced immune thrombotic thrombocytopenia syndrome (VITT), 745
COVID-associated movement disorders, 594
C-reactive protein (CRP), 510, 543, 640, 688
Crohn's disease (CD), 261, 262, 459, 640
  assessment, 465
  clinical manifestations, 466
  criticism on diagnostics criteria, 468
  diagnostic criteria, 467
  inflammatory effect, 466
  laboratory findings, 466, 467
  pathophysiology, 465
  prediction, 468
  prevalence and incidence, 465
  serological markers, 467, 468
  symptoms related to, 466
  therapy and prevention, 468, 469
Cryoglobulinemia, 199
Cryoglobulinemic syndrome, 195–197, 201
  brouet classification, 196
  classification criteria, 200
  clinical manifestations, 196, 197
  diagnosis, 198–200
  differential diagnosis, 200
  epidemiology, 196
  histopathology, 198
  laboratory features, 197
  treatment, 201
Cryptogenic organizing pneumonia (COP), 542
Cutaneous arteritis, 220
Cutaneous autoimmune bullous diseases, 490
Cutaneous leukocytoclastic angiitis (CLA), 219
Cutaneous lichen planus, 515
Cutaneous lupus erythematosus (CLE)
  classification, 482
  diagnostic criteria
    clinical manifestations, 482, 483
    direct immunofluorescence, 483, 484
    disease area and severity index, 485
    histology, 483
    laboratory parameters, 484
    organ-specific diagnostics and interdisciplinary investigations, 484
    photoprovocation, 484
  differential diagnosis, 485
  epidemiology, 481
  pathogenesis, 481
  prevention and treatment, 485, 486
  signs and symptoms, 485
Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), 485
Cyanocobalamin deficiency (CD), 705
Cyclic guanosine monophosphate (cGMP), 554
Cyclophosphamide, 646
Cyclosporin A (CsA), 570, 646, 677, 714, 720
Cytogenetic abnormalities, 719
Cytokines, 505
Cytotoxic immunosuppressive drugs, 547
Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), 398

D
Dactylitis, 502
Dapagliflozin, 677, 678
Dapsone, 513
Dawson's fingers, 563
Dense deposits disease (DDD), 682, 683
Deep infiltrating endometriosis (DE), 401
Delta/Notch-like epidermal growth factor-related receptor (DNER), 574
De Quervain´s thyroiditis, *see* Subacute thyroiditis (SAT)
Dermatomyositis (DM), 231, 234
  auto-antibodies, 234, 235
  clinical manifestations, 232, 233
  cutaneous manifestations, 233, 236
  diagnostic and classification criteria, 235–238
  epidemiology, 232
  muscle damage, biomarkers of, 233, 234
  pathogenesis, 232
  pathological features, 233
  prognosis, 238, 239
  therapy, 238
Dermoscopic examination of vitiligo, 498
Desmoglein 1, 490
Desquamative interstitial pneumonia (DIP), 542
Devic's syndrome, *see* Neuromyelitis optica (NMO)
Diabetes mellitus (DM)
  autoimmune diabetes/type 1A diabetes
    characteristics of T1DE1 and and T1DE2, 372
    clinical management, 371, 372
    early stages, 371
    etiopathogenesis, 368–370
    pathophysiology, 371
    prevention of beta-cell destruction, 372
  classification, 367
  definition, 367
  diagnosis, 367
  diagnosis criteria for, 367
  etiological classification of, 368
  insulin-dependent diabetes induced with checkpoint inhibitors, 373
  latent autoimmune diabetes of adulthood, 373
Diagnostic Criteria for VKH Disease (DCV), 646
Diagnostic criteria, definition of, 56
Diamond-Blackfan anemia, 718
Diffuse eosinophilic myositis, 269
Diffuse photoreceptor degeneration, 635
Diffuse single-organ vasculitis, 213, 214
  cutaneous arteritis, 220
  cutaneous leukocytoclastic angiitis, 219
  isolated retinal vasculitis, 220
  other cutaneous single-organ vasculitis, 220
  primary central nervous system vasculitis, 218–220
Diffusing capacity of the lungs for carbon monoxide (DLco) test, 544
Dilated cardiomyopathy (DCM), 525
  diagnostic criteria, 527, 528
  echocardiographic criteria, 527

  epidemiology, 526
  idiopathic, 525
  incidence, 526
  laboratory findings, 526
  pathogenesis, 525
  prediction of onset, 528
  prognosis, 528
  serological circulating autoantibodies, 526
  signs and symptoms, 526
  symptoms and signs, 526
  therapy and prevention, 528, 529
Diminished ovarian reserve (DOR) patients, 409
Diplopia, 652
Direct antiglobulin test (DAT), 699, 701
  negative, 701, 702
  positivity for IgG, 701
  positivity only for complement, 701
  sensitivity, specificity, and predictive value of, 702
Direct immunobead binding assay, 414
Direct immunofluorescence (DIF), 483, 484, 491, 492
Direct oral anticoagulants (DOAC), 16
Direct staining techniques, 590
Direct-acting antivirals (DAA), 196
Discoid lupus erythematosus (DLE), 483
Disease-modifying anti-rheumatic drugs (DMARDs), 503
Disease-modifying therapies (DMT), 565
Disorders of sex development (DSD), 407
Dissemination in space (DIS), 564
Dissemination in time (DIT), 562
Distal interphalangeal (DIP) joints, 502
Disturbed bone remodeling, 503
Double-seronegative generalized MG, 569
Drug (or herbal)-induced liver injury (DILI), 422
Drug-induced autoimmunity (D-IA), 75
  clinical manifestations, 76, 77
  diagnostic criteria, 77, 78
  epidemiology, 75
  pathogensis, 76
  prediction, 78
  prognosis, 78
  serological features, 77
  therapy, 78
Drug-induced interstitial pulmonary disease, 541
Dural/meningeal tail, 383
Düsseldorf classification, 482
Dysautonomia, 611
Dysferlin deficiency, 226
Dysphagia, 617
Dysphagia screening, 244

E
Ear chondritis, 62
Eculizumab, 694
Edrophonium (Tensilon, Enlon) test, 569
Efgartigimod alfa, 570
Electrocardiography, 526
Electromyography (EMG), 258
Electron microscopy (EM), 242, 665, 675
ELISPOT analysis, 598
Emerging targeted therapies, 499
Emicizumab, 750
Encephalitis, *see* Autoimmune encephalitis (AE)
Endocapillary cellularity, 658
Endolymphatic hydrops, 599
Endometrial stem cells implantation, 402
Endometriosis
  associated or high risk comorbidities, 403, 404
  associated symptoms, 403
  DE, 401
  definition, 401
  diagnosis, 404
  epidemiology, 402
  etiopathogenesis, 402, 403
  inflammatory disease, 403
  OMAs, 401
  pain syndromes, 403
  phenotypes, 401
  prevention, 405
  risk factors, 402
  serologic features and biomarkers, 404
  SUP, 401
  theories, 402
  therapy, 404, 405
Endometriosis Fertility Index (EFI), 401
Endometriotic implants, 403
Endometriotic lesions, 403
Endomyocardial biopsy, 527
Endoscopic retrograde cholangiopancreatography (ERCP), 429, 435, 436
Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), 445
Endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB), 445
Endoscopy, 467
Endothelin receptor antagonists (ERAs), 554
End-stage kidney disease (ESKD), 682
Enhanced depth imaging-OCT (EDI-OCT), 645
Enolase, 636
Enteric nervous systems (ENS), 611
Enthesitis-related arthritis (ERA), 27
Enthesopathy, 501
ENZIAN classification, 401
Enzyme-linked immune absorbent spot (ELISPOT), 477
Enzyme-linked immunosorbent assays (ELISA), 429, 664, 744, 749
Eosinophilia, 274, 319
Eosinophilic fasciitis (EF), 271, 272
  classification, 272
  diagnostic criteria, 272
  diagnostic imaging, 274
  epimysium, 273
  Groove sign, 272
  laboratory findings, 274
  main signs and symptoms, 273
  major and minor criteria, 274
  peau d'orange, 272
  perimyositis, 272
  therapy and prevention, 274
Eosinophilic granulomatosis with polyangiitis (EGPA), 77, 139, 141
  clinical manifestations, 141, 143, 144
  complementary investigations, 144
  diagnosis, 144, 145
  differential diagnosis, 145, 146
  epidemiology, 140, 141
  genetic predisposition, 139, 140
  immune dysregulation, 140
  maintenance therapy, 149
  pathophysiology, 139
  prevention, 150
  prognosis, 146, 147
  therapeutic strategies, 148
  treatment, 148

Eosinophilic myositis (EM), 267
  classification, 268, 270
  diagnostic criteria, 269–270
  diffuse eosinophilic myositis, 269
  eosinophilia-associated myopathy, 268
  eosinophilic fasciitis, 268
  eosinophilic major basic protein, 268
  eosinophilic perimyositis, 267, 269
  focal eosinophilic myositis, 269
  inflammatory myopathy, 267
  laboratory findings, 269
  serological markers, 269
  therapy and prevention, 270
Eosinophilic perimyositis, 269
Epidermal necrolysis, 519
Epididymo-orchitis, 414
Epilepsy, 629
Epoetin 2 (Eprex)-induced PRCA, 718
Epoprostenol, 553
Epstein Barr virus, 565, 718
Ertapenem, 513
Erythema annulare centrifugum (EAC), 517
Erythema multiforme (EM), 516
  clinical presentation, 517
  diagnosis, 517
  management, 518
  pathogenesis, 516
Erythrocyte sedimentation rate (ESR), 32, 543
Erythroderma, 520
Erythropoietin insufficiency, 699
Erythrosedimentation rate (ESR), 532
Estrogen deficiency, 410
Estrogen deprivation, 407
EULAR/ACR criteria, 237, 238
European Academy of Dermatology and Venereology (EADV), 485
European Consensus Lupus Activity Measurement (ECLAM), 485
European Reference Network in Hepatological Rare Diseases (ERN-LIVER), 422
European Scleroderma Trial and Research (EUSTAR), 42
Excessive daytime sleepiness (EDS), 621
Expanded disability score (EDSS), 584
Experimental autoimmune oophoritis (EAO), 409, 410, 415
Experimental autoimmune orchitis (EAO), 415
Expert PH unit, 551
Extrapulmonary sarcoidosis, 284
Eye redness, 639

F

Faciobrachial dystonic seizures (FBDS), 607, 624
Fahr's syndrome, 391
Familial dilated cardiomyopathy, 527
Familial interstitial pneumonias (FIP), 544
Familial mediterranean fever (FMF), 189, 295
  amyloidosis, 296
  classification criteria, 298, 299
  clinical manifestation, 295, 296
  diagnosis, 296, 297
  diagnostic criteria, 297–299
  genetics, 296
  laboratory findings, 296
  MEFV mutation, 296, 298, 299
Familial pulmonary fibrosis (FPF), 541
Fanconi syndrome, 688
Fatigue, 729
Fc-gamma receptor (FcγR)II, 724
Fc-gamma receptor (FcγR)IIIb, 725
Fecal calprotectin, 466
Felty’s syndrome (FS), 724
Fertility, 410
Fibrinoid necrosis, 684
Fibromyalgia (FM), 309, 310
  AAPT Diagnostic Criteria for, 313
  ACTTION-APS Pain Taxonomy Criteria, 314
  American College of Rheumatology 1990 classification criteria, 309, 310
  criteria 2016 revisions, 312–313
  definition of, 309
  diagnostic criteria, 310–312
  2016 revised criteria, 312, 314
  somatic symptoms, 310
Fibromyalgia symptom scale (FS scale), 312
Fibromyalgia Working Group, 314
Flow cytometry, 745
Flow cytometry tetramer technology, 477
Fluid-attenuation inversion recovery (FLAIR) sequences, 619
Fluorescein angiography, 636
18-Fluorodeoxyglucose positron emission tomography (FDG-PET) scanning, 617
Fluorohydrocortisone, 378
Focal eosinophilic myositis, 269
Focal single-organ vasculitis, 213, 214
  abdominal structures, 218
  breast, 215–216
  gynecologic vasculitis, 216–217
  isolated aortitis, 214–215
  male genital structures, 217–218
Focal segmental glomerulosclerosis (FSGS), 669, 673
  clinical presentation, 674
  epidemiology, 674
  evolution, 674, 675
  hereditary, 676
  pathogenesis and biomarkers, 675
  pathology, 675
  pathophysiological mechanisms, 676
  podocytopathies, 673
  primary forms, 676, 677
  prognostic factor, 675
  relapse after RT of primary forms, 678
  secondary forms, 677, 678
  treatment, 676
Forced vital capacity (FVC), 544
Formal autonomic testing, 612
Fresh frozen plasma (FFP), 751
Functional system scores (FSS), 584

G

Gabapentin, 631
Gadolinium-enhancing lesions, 563
Gait ataxia, 616, 617
Galactose-deficient IgA (Gd-IgA1) 1, 658
Gallium whole-body scan, 642
Gallstones, 430
Gamma-aminobutyric acid (GABA) inhibitory system, 594
Gamma-aminobutyric acid (GABA) type B receptor (GABABR), 573, 606
Gamma-enolase, 384
Ganglion cell trans-synaptic atrophy, 636
Ganglionic α3 subunit—nicotinic acetylcholine receptor (gAChR), 612
Gastric atrophy, 707
Gastric cancer, risk of, 453
Gastric carcinogenesis, 453

GD-associated dermatophaty, 357
Generalized pain, 312
Genetic cerebellar ataxias, 616
Genetic risk scores (GRS), 371
Genetic testing, 713
Genetic/epigenetic theory, 402
Genome-wide association studies (GWAS), 4, 38
GH deficiency, 382
Giant cell arteritis (GCA)
  clinical manifestations, 92
  diagnostic criteria, 93–96
  epidemiology, 92
  pathogenesis, 92
  treatment, 96
Glandulae renis incumbents, 375
Glomerular basement membrane (GBM), 135, 663, 676
Glomerular filtration barrier (GFB), 670, 676
Glomerular filtration rate (GFR), 677
Glomerular hyperfiltration, 677
Glucocorticoids (GC), 94, 113, 114, 238, 258, 264, 274, 446, 547, 671
Glucocorticoid therapy, 215
Glucocorticosteroids, 552
Glutamic acid decarboxylase (GAD) antibodies, 574, 618
Glutamic acid decarboxylase 65 (GAD65), 629
Gluten ataxia (GA), 619
Gluten-free diet (GFD), 471, 477, 478
Goldmann perimetry, 636
Gonadal dysgenesis, 407
Goodpasture’s syndrome, 173, 174
  clinical findings, 174
  diagnostic criteria, 174
  serological marker, 174
  treatment, 175, 176
Graft-versus-host disease (GVHD), 519, 714
  clinical findings, 520
  diagnosis, 520
  differentiation, 520
  management, 521
Graham-Steel murmur, 550
Granulocyte agglutination test (GAT), 725
Granulocyte colony-stimulating factor (G-CSF), 724
Granulocyte immunofluorescence test (GIFT), 725
Granulomatosis with polyangiitis (GPA), 120, 131
  clinical manifestations, 134
  diagnosis, 135–137
  epidemiology, 131
  organ manifestations, 134
  physiopathology, 132
  prognosis, 137, 138
  treatment, 137
Granulomatous hypophysitis (G-H), 384
Granulomatous lesions, 689
Granulomatous myositis (GM), 261
  aetiology, 261
  antimitochondrial autoantibody, 262
  autoimmune disorders, 262
  clinical manifestations, 262
  Crohn disease, 262
  diagnosis, 263
  epidemiology, 261
  etiology, 261
  Hashimoto thyroiditis, 262
  imaging, 263
  inclusión body myositis, 262
  myasthenia gravis, 262
  pathological features, 263
  prognosis, 264
  sarcoidosis, 262
  therapy, 264
Graves' orbitopathy, 651
Graves’ disease (GD), 355, 707
  clinical manifestations, 357
  daignosis and screening, 358, 359
  epidemiology, 355, 356
  extrathyroidal manifestations, 357
  immunopathogenesis, 356, 357
  major symptoms, 357
  physical signs, 357
  risk factors, 356
  treatment, 359
Gross hematuria, 656
Group A streptococcal (GAS) infections, 593, 594
Guillain-Barre syndrome (GBS), 578
  clinical course, 579, 580
  diagnosis, 580, 581
  epidemiology, 578
  etiology and pathogenesis, 579
  pathophysiology, 579
  treatment, 581, 582
Guselkumab, 513
Gut microbiome, 438
Gynecologic vasculitis, 216–217

H
Haptocorrin, 706
Hashimoto’s thyroiditis, 395
Heart-specific autoantibodies, 526
Heat shock proteins (HSPs), 536
Helicobacter pylori, 451
Hematopoietic stem cell transplant (HSCT), 570, 713, 714
Hemeralopia, 637
Hemolysis markers, 700
Hemolytic uremic syndrome (HUS), 691
  atypical, 736, 737
  diagnostic criteria, 737
  incidence, 734
  typical, 736, 737
Heparin-induced platelet activation assay (HIPA), 744
Heparin-induced thrombocytopenia (HIT), 741
  clinical features of, 743
  diagnosis, 743, 744
  4T score, 743
  incidence, 742
  laboratory test for anti-PF4 antibodies, 744, 745
  pathophysiology, 742
  treatment, 745, 746
  type I, 741, 742
  type II, 741, 742
Heparins, 750
Hepatosplenomegaly, 713
Hepatitis B virus (HBV)-associated vasculitis, 217
Hereditary focal segmental glomerulosclerosis, 673, 676
Hereditary thrombocytopenia, 729
Hermaphroditism, 407
Hidradenitis suppurativa (HS), 509
  associated diseases and differential diagnoses, 512, 513
  clinical manifestations and ultrasound signs, 510–512
  complications, 512
  diagnostic criteria, 513
  genetic tests, 510
  microbiology, 510
  serological markers, 510
  therapy and prevention, 513, 514

Hidradenitis suppurativa physician global assessment (HS-PGA), 512
Hidradenitis suppurativa severity index (IHS4), 512
High-density lipoprotein (HDL), 536
Highly active antiretroviral therapy (HAART), 341
High-resolution computed tomography (HRCT), 544
Hodgkin lymphoma, 571
Hodgkin's disease, 723
Holohaptocorrin, 706
Holotranscobalamin, 706
Homogeneous disease, 371
Hormone replacement therapy (HRT), 410
Hot spot, 388
Human epididymis protein (HE)-4, 404
human epithelioma cells (HEp-2) cells, 423
Human Genome Epidemiology Network (HuGENet), 531
Human immunodeficiency virus (HIV), 542
Humoral (autoantibody) response in SNHL, 599, 600
Hurley scale, 512
Hybrid closed-loop systems, 372
Hydroxychloroquine (HCQ), 8, 486, 637
Hypercoagulability, 670
Hypereosinophilic syndrome (HES), 146
Hypergammaglobulinemia, 701
Hypergastrinemia, 454
Hyperpigmentation, 376
Hypersegmentation, 707
Hypersegmented neutrophils, 707
Hypersomnia, 621
Hypertension, 664
Hyperthyroidism, 357, 358, 362–364
Hypoalbuminemia, 666, 670
Hypocalcemia, 391
Hypocomplementemia C3, 683
Hypocomplementemic UV (HUV), 203
  clinical presentation, 204, 205
  diagnosis, 207
  diagnostic criteria, 210
  differential diagnosis, 207–210
  epidemiology, 204
  histopathology, 206
  laboratory findings, 206
  pathophysiology, 204
  treatment, 210, 211
Hypomagnesemia, 390
Hyponatremia, 376
Hypoparathyroidism, 396
Hypophysitis, 381
  anti-PIT1 hypophysitis, 385
  classification, 383–385
  clinical manifestation, 381, 382
  diagnostic criteria, 382, 383
  granulomatous hypophysitis, 384
  IgG4-hypophysitis, 385
  immune checkpoint inhibitor-induced hypophysitis, 385
  Ly-H, 383, 384
  necrotizing hypophysitis, 385
  prevalence of, 381
  treatment, 382, 383
  xanthomatous hypophysitis, 384
Hyposthenuria, 688
Hypothalamus-pituitary-gonadal axis, 414
Hypothyroidism, 339, 361, 362, 364

I
Idiopathic adrenal insufficiency, 395
Idiopathic chronic hypoparathyroidism, 387
Idiopathic dilated cardiomyopathy, 525
Idiopathic duct-centric pancreatitis (IDCP), 442, 443
Idiopathic inflammatory myopathy (IIM), 225, 227, 228, 231, 232, 234–238, 255
Idiopathic interstitial pneumonias (IIPs)
  classification, 541–543
  clinical manifestations, 543
  diagnostic approach
    biomarkers, 543, 544
    bronchoscopy, 544, 545
    lung biopsy, 545
    lung function tests, 544
    multidisciplinary approach, 546
    radiology, 544
  treatment options, 546, 547
Idiopathic nonspecific interstitial pneumonia (NSIP), 541
Idiopathic pleuroparenchymal fibroelastosis, 542
Idiopathic pulmonary fibrosis (IPF), 541
Idiopathic thrombocytopenic purpura, 727
IgA nephropathy (IgAN), 189, 655
  acute kidney injury, 656
  asymptomatic hematuria and proteinuria, 656
  biomarkers, 658, 659
  chronic kidney disease, 656
  clinical course, 655, 659
  clinical presentation, 656
  diagnosis of, 658
  electron microscopy, 657
  epidemiology, 655, 656
  immunofluorescence findings, 657
  light microscopy, 657
  malignant hypertension, 656
  management of, 660
  MEST Score, 658
  nephrotic syndrome, 656
  Oxford classification, 657, 658
  pathogenesis of, 659
  pathology, 657
  pregnancy and, 657
  progression factors, 659
  rapidly progressive glomerulonephritis, 656
  Schönlein-Henoch purpura, 657
  secondary forms of, 657
  synpharyngitic macroscopic hematuria, 656
  treatment, 659–661
IgG antibodies, 599
IgG4-hypophysitis (IgG4-H), 382, 385
IgG4-related disease (IgG4-RD)
  autoimmune fibro-inflammatory disorder, 317
  clinical manifestations, 318, 319
  diagnostic criteria, 319, 320
  epidemiology, 317
  idiopathic retroperitoneal fibrosis, 317
  pathological findings, 319
  pathophysiology, 317
  prognosis, 320
  radiological findings, 319
  serological findings, 319
  treatment, 320, 321
IL-1 antagonist (anakinra), 601
Iloprost, 553
Imlifidase, 176
Immune checkpoint inhibitors (ICI), 329, 341
  arthritis, 330, 332
  clinical approach, 334

  - clinical manifestations, 329, 330
  - differential diagnosis, 333, 334
  - myositis, 332
  - rheumatic and systemic syndromes, 330, 334
  - rheumatic immune-related adverse events, 330, 331
  - sarcoidosis, 333
  - Sicca syndrome, 332, 333
  - vasculitis, 333
- Immune checkpoint inhibitor-induced hypophysitis, 385
- Immune complexes (ICs), 723
- Immune thrombocytopenia (ITP), 727
  - annual incidence, 728
  - classification, 728
  - clinical manifestations, 729
  - definition of, 727
  - diagnostic criteria, 729, 730
  - management, 731
  - primary, 728
    - complement, 729
    - defects in antigen-presenting cells and T-reg deficiency, 728, 729
    - pathologic antiplatelet antibodies, 728
  - prognosis, 730
  - secondary, 729
  - treatment, 731
- Immune-checkpoint inhibitor (ICI)-induced hypophysitis (ICI-H), 382
- Immune-mediated autonomic and sensory neuropathy, 612
- Immune-mediated necrotizing myopathy (IMNM), 255
  - clinical features, 256
  - complementary techniques, 258
  - diagnosis and classification, 257
  - epidemiology, 255
  - etiopathogenesis, 255, 256
  - histology, 257
  - laboratory, 256, 257
  - muscle biopsy, 258
  - muscle strength, 257
  - prognosis, 259
  - subtypes, 255
  - treatment, 258, 259
- Immune-mediated neuropathies, 578
- Immunofixation, 671
- Immunofluorescence, 658, 665, 671, 689
- Immunoglobulin A vasculitis (IgAV), 187–189, 192
  - classification criteria, 191
  - clinical manifestations, 188, 189
  - diagnosis, 190
  - differential diagnosis, 190
  - epidemiology, 187
  - laboratory findings, 190
  - pathogenesis, 188
  - treatment, 192
- Immunological tests, 664
- Immunomodulatory drugs, 570
- Immunoreceptor tyrosine-based activation motif (ITAM)-dependent signaling pathway, 742
- Immunosuppressants, 684
- Immunosuppressive drugs/therapy (IS), 59, 456, 527, 552, 666, 673, 675, 720, 750
- Immunosuppressive treatment, 666
- Immunotherapy, 608, 620, 624, 629, 631
- 2012 International Chapel Hill Consensus Conference (CHCC), 214
- In vitro fertilization (IVF), 405
- INBUILD trial, 59
- Inclusion body myositis (IBM), 226, 262
- Indexed stroke volume, 552
- Indirect antiglobulin test (IAT), 701
- Indirect immunofluorescence (IIF) assay, 388, 491
- Indocyanine green angiography (ICGA), 645
- Infectious folliculitis, 512
- Inflammation, 535, 537–539
- Inflammatory bowel disease (IBD), 287–289, 459, 460, 640
- Inflammatory cerebral amyloid angiopathy (ICAA), 590
- Inflammatory myopathy, *see* Sporadic inclusion body myositis (sIBM)
- Infliximab, 642, 647
- Influenza vaccine, 579
- Infratentorial lesions, 563
- Infrequent neuronal antibodies, 618, 619
- Innate immunity, 496, 535
- Insomnia, 621
- Insulin, 367
- Insulin-dependent diabetes induced with checkpoint inhibitors, 373
- Interface-dermatitis, 483
- Interferon γ (IFNγ), 496
- Interferon (IFN)-c-secreting T cells, 477
- Interferons autoantibodies (IFNsAbs), 388, 389
- Interleukin-23/interleukin-17, 503
- Intermittent cutaneous LE (ICLE), 482, 483
- International Working Group on ITP (IWG), 729
- Interstitial keratitis, 183, 185
- Interstitial lung disease (ILD), 248, 542, 543, 545
- Interstitial pneumonia with autoimmune features (IPAF), 542, 543
- Intracellular/onconeuronal antigens, 604
- Intracranial hemorrhage (ICH), 729
- Intracranial hypertension, 619
- Intracytoplasmic sperm injection (ICSI), 416
- Intraepithelial lymphocytes with T-cell receptor (TCR γδ+), 477
- Intraocular antiangiogenic drug therapy, 647
- Intrascrotal testicular masses, 414
- Intravascular hemolysis, 700
- Intravascular lymphoma (IVL), 590
- Intravenous immunoglobulin (IVIg), 631, 729
- Intrinsic factor (IF), 705
- Intrinsic factor antibodies (IFAs), 454, 705, 706, 708
- Invasive procedures, 554
- Iscalimab, 359
- Isolated aortitis, 214–215
- Isolated PRCA, 718
- Isolated retinal vasculitis, 220

J

- JAK1 expression, 496
- Janus kinase (JAK) inhibitors, 507
- Juvenile idiopathic arthritis (JIA), 25, 26
  - biologic classification, 28
  - classification, 34
  - clinical manifestations, 32
  - course, 33
  - diagnosis, 34, 35
  - differential diagnosis, 34
  - 2001 ILAR classification, 27
  - laboratory findings, 32, 33
  - pharmacologic treatment, 29
  - PRINTO Preliminary Criteria, 28
  - radiographic findings, 33
  - treatment, 28, 29, 35
- Juvenile idiopathic arthritis (JIA), 640, 641
- Juvenile-onset spondyloarthropathy, 289
- Juxtacortical or cortical lesions, 563

K
Kahn's criteria, 57
Kasukawa's criteria, 57, 58
Kawasaki disease (KD), 177–179
  clinical manifestations, 178
  diagnostic criteria, 179
  differential diagnosis, 179
  echocardiography, 178
  epidemiology, 177
  exanthema, 178
  laboratory findings, 178
  pathogenesis, 177
  treatment, 180
KDIGO guidelines, 659
Keratic precipitates (KPs), 640
Keratinocytes, 496
Kidney transplantation, 676
Krebs Von der Lungen 6 (KL-6), 543

L
Lactate dehydrogenase (LDH), 705
Lambert-Eaton myasthenic syndrome (LEMS), 572, 707
Large granular lymphocyte (LGL) leukemia, 723
Large-vessel vasculitis, 107
Latent autoimmune diabetes of adulthood, 373
Latent autoimmunity, 86
Lateral flow immunoassay (LFIA), 744
Latex immunoassay (LIA IgGAM), 744
LE profundus/panniculitis (LEP), 483
Left bundle branch block (LBBB), 526
Lennard-Jones criteria, 460, 467, 468
Leukocyte migration inhibition (LMI), 598
Lichen planus (LP), 515
  clinical findings, 515, 516
  cutaneous, 515
  diagnosis, 516
  key features, 516
  management, 516
Light microscopy, 664, 671
Light transmission aggregometry (LTA), 745
Limbic encephalitis (LE), 573, 606, 607
Lipoprotein receptor–related protein 4 (LRP4), 568
Liver biopsy, 423, 436, 437
Liver transplant (LT)-free survival, 431
Lobular lymphocytic panniculitis, 483
Löfgren's syndrome, 280
Low molecular weight heparin (LMWH), 741, 745
Low-density lipoprotein (LDL), 535
Low-grade coeliac enteropathy, 477
Lrp4 antibody–associated MG, 569
Lumbar punction, 584
Lumbar puncture, 590
Lung biopsy, 545
Lung function tests, 544
Lung transplantation, 547, 554
lupus anticoagulant (LA), 11, 749, 750
Lupus band test (LBT), 483
Lupus erythematosus (LE), 481
Lupus erythematosus tumidus (LET), 483
Lupus nephritis, 4
Lymphadenopathy, 713
Lymphatic and vascular metastasis theory, 402
Lymphocytic adenohypophysitis (LyA-H), 382
Lymphocytic hypophysitis (Ly-H), 381, 383, 384
Lymphocytic infundibuloneurohypophysitis (LyIN-H), 382
Lymphocytic panhypophysitis (LyP-H), 382, 384
Lymphoid interstitial pneumonia (LIP), 542
Lymphoplasmacytic infiltration, 441
Lymphoplasmacytic sclerosing pancreatitis (LPSP), 442

M
Macitentan, 554
Macrocytic anemia, 708
Macrocytic cells, 705
Macrocytosis, 707, 708
Macrophages, 503
Magnetic resonance cholangiopancreatography (MRCP), 429, 435
Magnetic resonance imaging (MRI), 235, 258, 274, 305, 404, 435
Major adverse cardiovascular events (MACE), 539
Major histocompatibility complexes (MHC), 728
Male infertility, 413, 416
Malignant hypertension, 656
Mammary vasculitis, 215
McAlpine, Lumsden, and Acheson criteria, 562
McDonald criteria, 562, 564, 565
Mean corpuscular hemoglobin (MCH), 707
Mean corpuscular hemoglobin concentration (MCHC), 707
Megakaryocytes, 728
Melanocytes, 496
Melanoma associated retinopathy (MAR), 635–637
Membranoproliferative glomerulonephritis (MPGN)
  characteristic features, 681
  clinical manifestations, 682
  diagnostic criteria, 684
  epidemiology, 681, 682
  pathogenesis, 682
  pathology, 683
  prognosis, 684
  serological characteristics, 683
  treatment, 684
Membranous nephropathy (MN), 663
  diagnosis of, 664, 665
  diseases associated with, 664
  Laboratory tests, 664
  primary, 663
  risk stratification, 665
  secondary, 663
  signs and symptoms, 664
  therapy, 666
Meniere's disease (MD), 598
Mepacrine, 486
Mesangial hypercellularity, 658
Mesangiocapillary glomerulonephritis, *see* Membranoproliferative glomerulonephritis (MPGN)
Metabolic dysfunction-associated steatotic liver disease (MASLD), 422, 423
Metabotropic glutamate receptors (mGluR), 618
Metastatic disease, 637
Methotrexate, 647
6-methyl mercaptopurine (6-MMP), 424
Methylprednisolone, 642, 689
Microangiopathic hemolytic anemia (MAHA), 692, 733
Microhematuria, 656
MicroRNAs, 676
Microscopic polyangiitis (MPA), 123, 127, 214
  classification, 128
  clinical features, 125
  clinical manifestations, 124
  diagnostic criteria, 127
  epidemiology, 123

  pathogenesis, 124
  pathological features, 125
  serological features, 126
  treatment, 128
Middle east respiratory syndrome coronavirus (MERS-CoV), 579
Migratory OM, 649
Mikulicz's disease, 385
Mild enteropathy CD, 477
Miller Fisher's syndrome (MFS), 578
Minimal change disease (MCD)
  diagnostic criteria, 671
  immunosuppressive treatment, 671
  incidence, 669
  laboratory findings, 670, 671
  nephrotic syndrome, management of, 672
  pathogenesis, 669
  signs and symptoms, 670
Mitogen-activated protein kinases (MAPKs), 526
Mixed connective tissue disease (MCTD), 55
  classification criteria, 56–58
    Alarcón-Segovia's criteria, 57
    critical analysis of, 58, 59
    definition of, 56
    Kahn's criteria, 57
    Kasukawa's criteria, 57
    Sharp's criteria, 56
    Tanaka's criteria, 58
  clinical shift, 55
  serological findings, 56
  therapy and prognosis, 59
Modified Ponticelli regimen, 666
Monoclonal antibodies, 585
Monoclonal gammopathy, 682, 684
Monocytes, 742
Montreal classification, 460
Montreal classification of Crohn's disease, 466
Morvan's syndrome, 612, 625
Mouth and genital ulcers with inflamed cartilage (MAGIC), 63
Movement disorders, 594
Moxifloxacin, 513
Müller cells, 636
Müllerian anomalies, 405
Mullerian remnant theory, 402
Multidisciplinary approach, 546
Multidisciplinary discussion, 546
Multifocal motor neuropathy (MNN), 581
Multiple autoimmune syndrome (MAS), 84
Multiple electrode aggregometry (MEA), 745
Multiple sclerosis (MS), 559, 560, 583
  ancillary test for, 560
  diagnostic criteria for, 561
    differential diagnosis of relapsing-remitting multiple sclerosis, 564, 565
    dissemination in space and time, 563, 564
    historical review, 561, 562
    objective clinical evidence, 563
    typical syndromes, 563
Mumps-measles-rubella (MMR) vaccine, 729
Muscle biopsy, 258
Muscle strength, 257
Muscle ultrasonography, 235
Muscle-specific tyrosine kinase (MuSK), 568
Muscular dystrophies, 226, 228
MuSK antibody-associated MG, 568
Myasthenia gravis (MG), 567
  clinical manifestations, 568
  diagnosis, 569
  distribution of weakness, 568
  double-seronegative generalized MG, 569
  due to antibodies against AChR, 568
  incidence and prevalence, 567
  Lrp4 antibody–associated MG, 569
  MuSK antibody-associated MG, 568
  pathophysiology, 567, 568
  thymoma-associated MG, 568
  treatment, 569, 570
Mycophenolate (MMF), 424
Mycophenolate mofetil (MMF), 570, 591, 647, 677, 694
Mycoplasma-induced rash and mucositis (MIRM), 517
Myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD), 560, 564
Myelin oligodendrocyte glycoprotein-antibody-seropositive inflammatory demyelinating disease, 583
Myelin oligodendrocyte glycoprotein (MOG), 584
Myelin oligodendrocyte glycoprotein (MOG) antibodies, 607
Myelodysplasia, 712
Myelodysplastic syndrome (MDS), 719
Myocarditis, 525
Myositis, 225, 227, 248, 332
Myositis-associated antibodies (MAA), 231, 234
Myositis-specific antibodies (MSA), 231, 234

N
NACHT leucine-rich-repeat protein-5 (NALP-5Abs), 388
NACHT, leucine-rich repeat, pyrin domain-containing protein 5 (NALP5), 396
Narcolepsy, 623
Narrow-band ultraviolet B (nbUVB) phototherapy, 499
Nasal chondritis, 62
Nebulized iloprost, 553
Necrotizing hypophysitis, 385
Neonatal Fc receptor antagonists, 570
Neoplasia, 664
Nephritic factor amplification loop (NFa), 683
Nephrotic syndrome (NS), 656, 661, 663, 669, 672, 673, 682
Neural antibodies, 607, 608
Neurodegenerative alpha-synucleinopathy, 612
Neurogenic disease, 226
Neuroimaging, 595
Neuromyelitis optica (NMO), 583
  clinical manifestation, 584
  diagnosis, 584, 585
  epidemiology, 583, 584
  etiology and pathogenesis, 584
  treatment, 585, 586
Neuromyelitis optica spectrum disorders (NMOSD), 564, 621, 623
Neuronal death, 707
Neuropsychiatric lupus (NPSLE), 589
Neurosarcoidosis, 281
Neutropenia, 723
Neutrophil infiltration, 503
Nijmegen Bethesda assay, 749
Nikolsky sign, 491
Nintedanib, 59, 546
NMO spectrum disorders (NMOSD), 583
Non-alcoholic steatohepatitis (NASH), 429
Non-paraneoplastic autoimmune retinopathy (npAIR), 635
Non-rapid-eye-movement sleep (NREM)
  parasomnia, 627
  sleep, 626
Nonsteroidal anti-inflammatory drugs (NSAIDs), 192, 535, 689
Nyctalopia, 637

O

Obesity, 659
Obeticholic acid (OCA), 428
Obliterative phlebitis, 319
Obstructive jaundice, 446
Occult ovarian insufficiency, 409
Oligoarticular varients, 501
Oligoclonal bands (OCB), 562, 606
Operative Link for gastric intestinal metaplasia (OLGIM) staging systems, 455
Operative link for gastritis assessment (OLGA), 455
Ophthalmopathy, 357
Opsoclonus-myoclonus syndrome (OMS), 574
Optic neuritis, 584
Optical coherence tomography (OCT), 645
Orbital myositis (OM), 649
  biochemical features, 650
  classification, 650
  clinical manifestations, 649
  diagnosis
    clinical criteria, 651
    compatible pathological examination, 651
    corticosteroids, response to, 651
    imaging criteria, 651
  diagnostic criteria, 651
  differential diagnosis, 651
  entities associated with, 650
  epidemiology, 649
  Imaging techniques, 650
  pathological features, 651
  treatment, 651, 652
Orchitis
  acute, 413
  chronic, 413
  signs and symptoms, 413
Organizing pneumonia (OP), 542
Organ-specific autoantibodies, 395
Ovarian endometriomas (OMA), 401, 404
Overt autoimmunity, 82, 86
Overt PolyA, 82
Oxford classification of IgAN, 657
Oxidative stress, 496, 538
Ozurdex, 642

P

Pain, definition of, 309
Pancreato-hepatobiliary disease, 318
Panuveitis, 639, 642
Paraclinical evidence, 562
Paraneoplasic vitelliform maculopathy, 635
Paraneoplastic autonomic syndromes, 612
Paraneoplastic cerebellar degeneration (PCD), 573, 574, 615, 617
Paraneoplastic encephalitis, 623, 624
Paraneoplastic encephalomyelitis (PEM), 573
Paraneoplastic neurological syndromes (PNS), 571, 603
  clinical manifestations, 572
  diagnostic criteria, 572, 574, 575
  high-risk for cancer neurological syndromes
    limbic encephalitis, 573
    OMS, 574
    paraneoplastic cerebellar degeneration, 573, 574
    PEM, 573
    sensory neuronopathy, 574
  intermediate-risk for cancer neurological syndromes, 574
  management and prognosis, 575
  neuronal antibodies, 572, 573
Paraneoplastic retinopathy syndromes (PR), 635, 636
Paraneoplastic syndromes (PNS), 635
Parasarcoidosis, 281
Parasympathetic nervous system (PNS), 611
Parietal cell antibodies (PCAs), 454, 705, 706
Parietal cells (PC), 705
Parkinson disease, 621
Paroxysmal cold hemoglobinuria (PCH), 699, 700
Paroxysmal nocturnal hemoglobinuria, 712
Particle gel immuno and immunofiltration assays (PaGIA and PIFA), 744
Parvovirus B19, 718, 719
Pathologic antiplatelet antibodies, 728
Peak oxygen consumption and ventilatory efficiency, 552
Pediatric Rheumatology International Trials Organization (PRINTO), 27
Pemphigus
  definition, 489
  epidemiology, 489
  foliaceus, 490
  pathogenesis, 489
Pemphigus vulgaris
  diagnostic criteria, 492
  mucocutaneous findings, 490
  pathological features, 491
  prognosis, 492
  treatment, 492, 493
Pepsin, 706
Percutaneous transluminal angioplasty (PTA), 113
Perimyositis, 272
Perinuclear antineutrophil cytoplasmic antibody (p-ANCA), 435, 460
Peripheral eosinophilia, 271
Peripheral neuropathy, 707
Periventricular lesions, 563
Pernicious anemia (PA), 706
  clinical manifestations, 706, 707
  definition of, 705
  diagnostic criteria, 708
  epidemiology of, 705, 706
  hematologic features, 707
  history, 706
  pathogenesis, 706
  pathological features, 707
  pharmacological treatment of, 709
  prognosis, 708
  role of autoantibodies, 708
  serological and biochemical features, 707, 708
  therapeutic management, 709
Phosphodiesterase-5 Inhibitors, 554
Phospholipase A2 receptor (aPLA$_2$R), 664–666
Photoprovocation, 484
Phototesting, 484
Phototherapy, 498, 499
Pirfenidone, 546
Pituitary gland specific factor 1b (PGSF1b), 384
Plasma exchange (PE), 694
Plasma methylmalonic acid (MMA), 707
Plasma total homocysteine (tHC), 707–708
Platelet activation assays, 744
Platelet factor 4, 742
Platelet transfusions, 713
Platelet-type pattern, 729
Podocytopathies, 676
Point Body Manikin, 314
Polyarteritis nodosa (PAN), 115, 127, 200, 214, 217

- clinical manifestations, 116
- definition and classification, 119, 120
- diagnosis, 118, 119
- epidemiology, 116
- histopathological findings, 118
- laboratory features, 117
- pathogenesis, 116
- principal manifestations, 117
- prognosis, 121
- treatment, 121

Polyarticular pattern, 502
Polyautoimmunity, 82, 83
- autoimmune tautology, 85
- clinical significance, 85
- diagnostic criteria, 86
- immunological and genetical basis, 83, 84
- latent and overt, 84
- multiple autoimmune syndrome, 84, 85
- therapy, 86

Polygenic risk scores (PRS), 371
Polymorphic erythema, *see* Erythema multiforme (EM)
Polymorphonuclear neutrophil (PMN), 723
Polymorphous light eruption (PLE), 484
Polymyalgia rheumatica (PMR), 92, 99
- classification criteria, 101
- clinical manifestations, 100
- diagnosis, 102
- differential diagnosis, 103
- epidemiology, 99
- histopathology, 100
- imaging techniques, 100, 101
- laboratory findings, 100
- pathogenesis, 99, 100
- previous diagnostic, 104
- treatment, 104, 105

Polymyositis (PM), 225, 226, 542
- clinical manifestations, 226
- diagnosis, 227
- epidemiology, 225
- pathogenesis, 225
- pathology, 226
- serological features, 228
- treatment, 228
- types, 226–227

Polypharmacy, 689
Poser et al. criteria, 562
Positron emission tomography (PET), 538
Post-COVID, 580
Posterior reversible encephalopathy syndrome (PRES), 580
Posterior uveitis, 639
Postinfectious cerebellar ataxia, 619
Postpartum thyroiditis (PT), 343, 361
- approach, 362
- biomarkers, 362
- clinical manifestations, 363
- diagnostic algorithm, 363
- diagnostic criteria, 363
- epidemiology, 361
- functional thyroid tests, 362
- pathogenesis, 361, 362
- pathological features, 362
- prognosis, 364, 365
- treatment, 364

Potential alarm signs, 551
Prednisolone, 416
Prednisone, 424, 646
Pregnancy, 361–364
Pregnancy and IgA nephropathy, 657
Premature ovarian failure (POF), 407
Premature ovarian insufficiency (POI), 407
- and other autoimmune diseases, 408
- incidence, 407
- isolated, 408
  - cellular immunity alterations in patients with, 409
  - ovarian histology in patients with, 409
  - signs of autoimmunity, 408, 409
- treatment, 410

Primary angiitis of the CNS [PACNS], 587
Primary autoimmune cerebellar ataxia (PACA), 616
Primary autoimmune orchitis, 413–415
Primary biliary cholangitis (PBC)
- causes of, 429, 430
- definition of, 427
- diagnose
  - clinical and biochemical abnormalities, 429
  - Histologic abnormalities, 429
  - Immunological abnormalities, 429
- diagnostic criteria, 428
- histological stages of, 430
- laboratory and serological markers, 428
- mechanism targeted therapies, 431
- signs and symptoms, 428
- striking female preponderance, 428
- therapy and prevention, 430, 431
- UDCA, 428

Primary central nervous system vasculitis (PCNSV), 218–220, 587–589
- clinical manifestations, 588
- mimickers, 590
- MRI findings, 588
- treatment, 591

Primary focal segmental glomerulosclerosis (p-FSGS), 673, 674, 677
Primary hemolytic anemia (PHA), 705
Primary intracranial or cerebral vasculitis, 587
Primary membranous nephropathy (pMN), 663, 664, 725
Primary sclerosing cholangitis (PSC)
- cholangiocarcinoma, 438
- diagnosis, 433
- diagnostic criteria, 435
  - ERCP, 435, 436
  - liver biopsy, 436, 437
  - MRI/MRCP, 435, 436
- genetic predisposition, 433
- laboratory tests and serology, 434, 435
- liver biochemistry indicative, 435
- risks of, 434
- signs and symptoms, 434
- therapy and prevention, 438
  - anti-fibrotic agent, 438
  - biochemistry, 438
  - cancer surveillance, 438
  - gut microbiome, modulating, 438
  - immunosuppressive drugs, 438
  - relieving biliary obstruction, 438
  - treating Pruritis, 438

Progressive encephalomyelitis with rigidity and myoclonus (PERM), 629
Progressive multiple sclerosis (PMS), 560
Progressive sensorineural hearing loss (PSNHL), 597, 598, 600
Propylthiouracil (PTU), 76
Prostacyclin, 553
Protease, 735

Protease-activated receptor 1 (PAR-1), 742
Proteinase-3 (PR3), 131
Protein tyrosine phosphatase, nonreceptor type 22 (PTPN22), 398
Proteinuria, 656, 660, 665, 689, 737
Pruritis, 438
PsA *sine* psoriasis, 501
Pseudo thrombocytopenia, 729
Pseudogranulomatous thyroiditis, *see* Subacute thyroiditis (SAT)
Psoriatic arthritis (PsA), 287, 288, 501
  arthritis mutilans, 502
  classification criteria, 502
  clinical spectrum, 501, 502
  distal pattern affecting distal interphalangeal joints, 502
  mechanisms, 503
  polyarticular pattern, 502
  treatment, 503
Psoriatic nail involvement, 502
Pulmonary arterial hypertension (PAH), 59, 549
  associated with systemic autoimmune disease, 550
  characterization, 549, 550
  clinical presentation
    medical history, 550
    physical signs, 550
  prognosis, 551
  risk stratification, 553
  screening for, 551
  treatment
    algorithm, 554, 555
    general measures, 552
    pharmacological treatment, 552–554
Pulmonary arterial pressure (PAP), 549
Pulmonary circulation, 549
Pulmonary hypertension (PH)
  concept, 549
  diagnosis, 550–552
  nomenclature and classification, 549
Pulmonary sarcoidosis, 280, 284
Pure red cell aplasia (PRCA), 717
  acquired, 718
  classification, 718
  clinical manifestations, 718
  diagnostic criteria, 719, 720
  differential diagnosis, 719
  etiology, 717
  laboratory findings, 719
  pathophysiology, 718
  prognosis, 720
  therapy, 720
Pyruvate dehydrogenase complex (PDC-E2), 427

Q
Quadriceps atrophy, 242
Qualitative tests, 744
Quality of life (QoL), 506
Quantiferon testing, 383

R
Radioligand binding assays, 384
Radiology, 544
Rapid-eye-movement sleep behavior disorder (RBD), 621
Rapid-eye-movement sleep (REM), 625, 626
Rapidly progressive glomerulonephritis (RPGN), 656
Ravulizumab, 694
Raynaud's phenomenon (RP), 40, 59, 67, 248, 250
  causes, 68
  classification, 68
  clinical manifestations, 69
  diagnostic criteria, 70
  differential diagnosis, 70
  epidemiology, 67
  pathogenesis, 68, 69
  pathological features, 69
  prognosis, 71
  therapeutic management, 71, 72
Reactive arthritis (ReA), 287, 288
Receiver operator curve (ROC), 423
Receptor activator of nuclear factor-kappa B ligand (RANKL), 503
Recombinant activated factor VII (rFVIIa), 750
Refractory sarcoidosis, 285
Regulatory T cells (Tregs), 396
Relapsing polychondritis (RP), 61
  autoimmune/inflammatory diseases, 65
  clinical manifestations, 62
  damage monitoring, 66
  diagnostic criteria, 64
  differential diagnosis, 65
  epidemiology, 61, 62
  laboratory features, 64
  pathogenesis, 62
  pathological features, 64
  prognosis, 65
  signs and symptoms, 63
  treatment, 65, 66
Relapsing-remitting multiple sclerosis (RRMS), 559, 564, 565
Renal survival, 684
Renal transplantation (RT), 673, 678
Renin-angiotensin aldosterone system inhibitors (RAASI), 673
Renin-angiotensin system (RAS), 68
Respiratory bronchiolitis–associated interstitial lung disease (RBILD), 542, 547
Respiratory insufficiency, 584
Retrograde menstruation theory, 402
Retroperitoneal fibrosis, 318
Reversible cerebral vasoconstriction syndrome (RCVS), 588, 590
Revised American Society for Reproductive Medicine (rASMR), 401
Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index (RCLASI), 485
Revised Diagnostic Criteria for VKH disease (RDC), 645–646
Revised Jones criteria, 532
Rheumatic chorea, 593
Rheumatic fever (RF), 531
  clinical manifestations, 533
  clinical presentation, 533
  definition of, 531
  diagnostic criteria, 532
  treatment, 534
Rheumatic heart disease (RHD), 531
Rheumatoid arthritis (RA), 19
  clinical presentation, 20, 21
  diagnosis, 22
  epidemiology, 19
  prognosis, 23
  risk factors, 20
  serological features, 21
  treatment, 23
Rheumatoid factor (RF), 21, 27
Right heart catheterization (RHC), 551
Riociguat, 554

Risankizumab, 513
Ritlecitinib, 507
Rituximab, 149, 591, 601, 647, 666, 677, 703, 739
Routine HIT-IgG screening, 745
Row of tombstones, 491
Ruxolitinib, 499

S
Sacroiliitis, 641
Salivary gland biopsy, 51
Sarcoidosis, 261, 262, 279, 333, 641, 642
  ancillary tests, 282, 283
  clinical presentation, 280
  diagnostic criteria, 283, 284
  epidemiology, 279
  etiology, 279, 280
  extrapulmonary sarcoidosis, 284
  heart involvement, 281
  immunopathogenesis, 280
  liver involvement, 281
  muscle involvement, 281
  neurosarcoidosis, 281
  ocular involvement, 281
  organ involvement, 280
  parasarcoidosis, 281
  parotid involvement, 281
  prognosis, 284
  pulmonary sarcoidosis, 284
  refractory sarcoidosis, 285
  reticuloendothelial system, 281
  signs and symptoms, 282
  skin, 280, 281
  therapy, 284
  treatment, 285
Sars-Cov-2 infections, 579
Sartorius Hidradenitis Suppurativa Score, 512
Scattered melanophages, 635
Schistocytes, 708, 734
Schmidt's syndrome, 397
Schönlein-Henoch purpura, 657
Schumacher et al. Criteria 1965, 562
Second hit hypothesis, 735
Secondary autoimmune orchitis, 413–416
Secondary central nervous system vasculitis (SCNSV), 587, 589, 590
Secondary focal segmental glomerulosclerosis, 673, 677, 678
Secondary forms of IgA nephropathy, 657
Secukinumab, 513
Segmental glomerulosclerosis, 658
Selexipag, 553
Semi-automated insulin infusion systems, 372
Sensory neuronopathy (SN), 574
Septin-5, 619
Seronegative spondyloarthropathies, 640
Serotonin-release assay (SRA), 745
Serum angiotensin converting enzyme, 383
Serum anti-proopiomelanocortin (POMC) antibodies, 385
Serum biomarker tests, 707
Serum ghrelin, 707
Severe cutaneous adverse drug reactions (SCAR), 518
Severe insomnia, 625
Severity of Alopecia Tool (SALT), 506
Shared autoimmunity, 395
Sharp's criteria, 56
Shiga toxin, 736
Short-term memory loss, 606
Sicca syndrome, 332, 333
Sildenafil, 554
Silent thyroiditis, 343
Simpharyngitic macrosopic hematuria, 658
Single-fiber electromyography, 569
Single muscle paresis, 578
Single nucleotide polymorphisms (SNPs), 68
Single-organ vasculitis (SOV)
  categorization of, 214
  definition, 214
  diffuse, 213, 214
    cutaneous arteritis, 220
    cutaneous leukocytoclastic angiitis, 219
    isolated retinal vasculitis, 220
    other cutaneous single-organ vasculitis, 220
    primary central nervous system vasculitis, 218–220
  focal, 213, 214
    abdominal structures, 218
    breast, 215–216
    gynecologic vasculitis, 216–217
    isolated aortitis, 214–215
    male genital structures, 217–218
6-min walk test, 552
6-thioguianine (6-TG), 424
Sjögren disease (SjS), 47–51, 519
Sjögren's syndrome (SS), 200, 404, 429, 451, 589, 611, 616, 723, 739
Skin biopsy, 498
Sleep breathing disorders, 623
Sleep disorders, 621
  anti-IgLON5 disease, 625, 626
  anti-LGI1 encephalitis, 624
  anti-NMDA receptor encephalitis, 624
  in autoimmune neurological disorders, 622
  EDS, 621
  Morvan's syndrome, 625
  narcolepsy, 623
  NMOSD, 623
  paraneoplastic encephalitis, 623, 624
  RBD, 623
  types of, 621
Small duct-primary sclerosing cholangitis (SD-PSC), 435
Small fiber neuropathy, 578, 579
Soft tissue bleeding, 747
Soluble guanylate cyclase (sGC) stimulators, 554
Soluble urokinase receptor (suPAR), 676
Sox10, 396
Spinal cord lesions, 563
Spinal variants, 501
Splenic macrophages, 728
Spondyloarthritis (SpA), 287, 501
  diagnostic criteria, 290, 291
  environmental aspects, 289
  incidence, 290
  juvenile-onset spondyloarthropathy, 289
  laboratory findings, 289
  pathogenesis, 289, 290
  prevalence, 290
  prevention, 292
  prognosis, 291, 292
  signs and symptoms, 288, 289
  treatment, 292, 293
  undifferentiated spondyloarthropathy, 289

Sporadic inclusion body myositis (sIBM)
  aetiopathogenesis, 242
  classification, 243
  cytoplasmic filamentous inclusions, 242
  description, 241
  diagnosis, 242
  diagnostic criteria, 243
  diagnostic criteria, criticism of, 243, 244
  differential diagnosis, 243
  laboratory findings, 243
  muscle biopsy, 242
  pathological features, 242
  prevention, 244
  quadriceps atrophy, 242
  serological markers, 243
  signs and symptoms, 243
  therapy, 244
St. Johannis chorea, 593
St. Vitus dance, 593
Stereotactic radiotherapy, 383
Steroids, 738
Steroid-sensitive nephrotic syndrome, 671
Stevens-Johnson's syndrome (SJS), 517–519
Stiff-person spectrum disorder (SPSD), 629
  auto-antibodies associated with, 630
  clinical characteristics, 629
  Dalaka's 2009 diagnostic criteria, 631
  with diabetes mellitus, 629
  electrophysiological findings, 630
  symptoms and sign, 629, 630
  therapeutic approach, 631
Stiff-person syndrome (SPS), 629
Still's disease, 640
Stool biomarkers, 466
Storiform fibrosis, 319
Stridor, 623
Subacute cutaneous lupus erythematosus (SCLE), 481–483
Subacute orchitis, 413
Subacute thyroiditis (SAT), 351
  biochemical features, 352
  clinical manifestations, 352
  diagnostic criteria, 352, 353
  main characteristics, 353
  pathogenesis, 351, 352
  prognosis, 353
  thyroid pain, 352
  thyrotoxicosis, 351–353
  treatment, 353
Subclinical hypothyroidism, 364, 365
Subcutaneous insulin, 372
Subepithelial deposits of IgA antitransglutaminase tissue, 477
Sudden sensorineural hearing loss (SSNHL), 597, 600, 601
Sugiura sign, 644
Sunset glow fundus, 644
Superficial peritoneal lesions (SUP), 401
Supervised exercise training programs, 552
Supportive measures, 554
Surgical lung biopsy (SLB), 545
Susac syndrome, 167–170
  brain involvement, 168
  clinical manifestations, 168
  diagnosis, 169
  epidemiology, 167
  eye involvement, 168
  history, 167
  laboratory findings, 169
  pathogenesis, 167, 168
  pathological features, 169
  prognosis, 170
  treatment, 170
  vestibulocochlear involvement, 169
Swallows, 509
Sydenham chorea (SC)
  diagnosis, 595
  etiology, 593, 594
  pathophysiology, 594, 595
  treatment, 595, 596
Sydney biopsy protocol, 455
Sympathetic nervous system (SNS), 611
Symptom severity (SS) scale, 311
Syndrome of inadequate antidiuretic hormone secretion (SIADH), 584
Synovial vascularity, 503
Synovitis, 33
Synpharyngitic macroscopic hematuria, 656
Synthetic prostacyclin, 553
Systemic erythematosus lupus (SLE), 200
Systemic lupus activity measure (SLAM), 485
Systemic glucocorticoids, 651
Systemic juvenile idiopathic arthritis (SJIA), 31
Systemic lupus erythematosus (SLE), 3, 481, 550, 723, 724
  classification, 7
  clinical manifestations, 4, 5
  diagnosis, 6, 7
  disease activity, 7, 8
  genetics, 4
  immunologic markers, 5, 6
  prevention, 8
  signs and symptoms, 5
  therapy, 8
Systemic Lupus Erythematosus Collaborating Clinics Group (SCLICC) criteria, 482
Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI), 485
Systemic sclerosis (SSc), 37, 399, 550
  antinuclear antibodies, 39, 40
  classification criteria, 52
  diagnostics criteria, 52, 53
  epidemiology, 38
  genetics, 38
  glandular dysfunction, 50
  glandular involvement, 48, 53
  immunological profile, 51
  laboratory findings, 38
  laboratory studies, 50
  LeRoy, 43
  malignancy, 44
  prevalence, 39
  salivary gland biopsy, 51
  sine scleroderma, 42
  skin subsets, 42
  symptoms, 49
  systemic manifestations, 40–42

T
Tacrolimus, 570, 666
Takayasu arteritis (TKA), 107, 110
  clinical manifestations, 108, 109
  diagnosis, 111–113
  disease activity assessment, 111
  epidemiology, 108
  etiopathogenesis, 108

  histopathology, 111
  laboratory findings, 109
  treatment, 113, 114
  vascular imaging techniques, 110, 111
Tanaka's criteria, 58, 59
T-cell-mediated autoimmunity in SNHL, 598
T-cell-mediated PRCA, 718
T-cells, 369
Temporal arteries, 92
Temporal artery biopsy (TAB), 93
Therapeutic plasma exchange (TPE), 738
Thromboangiitis obliterans (TAO), *see* Buerger's disease
Thrombocytopenia, 692, 729, 742, 743
Thrombospondin 7A type 1 protein (THSD7A), 663
Thrombotic microangiopathies (TMA), 691, 734
  classification, 734
  definition of, 733
  incidence, 734
Thrombotic thrombocytopenic purpura (TTP), 692, 742
  acquired and inhered, 735
  clinical manifestations, 736
  diagnostic criteria, 737
  history, 735
  incidence, 734
  prognosis, 739
  therapy, 738, 739
Thymoma-associated MG, 568
Thyroglobulin antibodies, 339
Thyroid acropachy, 357
Thyroid imaging, 358, 359
Thyroid peroxidase antibodies, 342
Thyrotoxicosis, 352, 353
Thyroxine, 339
Tizanidine, 631
Tocilizumab, 96
Tofacitinib, 486
Toll-like receptors (TLR), 324
Topical and systemic steroids, 499
Topical immunomodulators, 499
Total lung capacity (TLC), 544
Toxic epidermal necrolysis (TEN), 518, 519
Transbronchial lung biopsy (TBLB), 544
Transbronchial lung cryobiopsy (TBLC), 544
Transcobalamin, 706
Transmural inflammation, 588
Transplantation theory, 402
Transvaginal sonography (TVS), 404
T-reg deficiency, 728, 729
Treprostinil, 553
Trichoscopy, 506, 507
TSHR autoantibodies test, 358
TSH-R-blocking antibody, 359
TSH-R small-molecule ligands, 359
Tube test, 702
Tubular atrophy, 658
Tubulointerstitial compartment, 688
Tumor necrosis factor-alpha (TNF-α), 712
Tumor necrosis factor inhibitors (TNFi), 75
Type 1 diabetes (T1D), 82, 395
  characteristics of T1DE1 and and T1DE2, 372
  clinical management, 371, 372
  early stages, 371
  etiopathogenesis, 368–370
  pathophysiology, 371
  prevention of beta-cell destruction, 372
Type XVII collagen, 490

U
UBA1 gene, 302
Ulcerative colitis (UC), , , s, 459, 640
  biochemical and serological features, 460
  clinical manifestations, 459, 460
  diagnostic criteria, 460, 461
  extraintestinal manifestations, 460
  prediction, 462
  prognosis, 461
  therapy and prevention, 462
Ulcerative Colitis Endoscopic Index of Severity (UCEIS), 461
Ultra-large VWF (ULVWF), 735
Ultrasound (US), 274
Undifferentiated connective tissue disease (UCTD), 55
Unfractionated heparin (UFH), 741, 745
Unilateral anterior uveitis, 640
Universal vitiligo, 497
Urine protein-creatinine ratio (UPCR), 659
Ursodeoxycholic acid (UDCA), 428, 431, 438
Urticarial vasculitis (UV), 203
Ustekinumab, 513
Usual interstitial pneumonia (UIP), 541, 545
Uveitis, 639, 640
  Behçet uveitis, 641
  classification, 640
  idiopathic, 640
  inflammatory bowel diseases, 640
  JIA, 640, 641
  recurrence or chronicity, 644
  sarcoidosis, 641, 642
  treatment of noninfectious intermediate, posterior, or panuveitis, 639, 642
  Vogt–Koyanagi–Harada Syndrome, 641

V
Vaccine-induced immune thrombotic thrombocytopenia (VITT), 744
Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome, 301
  auricular chondritis, 304
  autoinflammation, 306
  bilateral pulmonary infiltrates, 304
  classification criteria, 307
  clinical manifestations, 302, 303
  cytoplasmic vacuoles, 304
  diagnostic criteria, 307
  differential diagnosis, 305
  epidemiology, 302
  genetics and pathophysiology, 302
  hematopathology, 305
  histopathology, 305
  hypermetabolic lung infiltrates, 304
  imaging techniques, 305
  laboratory changes, 305
  laboratory features, 304
  monogenic autoinflammatory diseases, 306
  postular skin lesions, 304
  prognostic factors, 306, 307
  relapsing polychondritis, 306
  systemic vasculitis, 306
  treatment, 307
Vagal nerve, 611
Valsalva maneuver, 612
Varicella-Zoster virus (VZV), 729
Vascular smooth muscle cells (VSMCs), 535
Vasculitic neuropathy, 578

Vasculitis, 333, 587
Ventilation-perfusion (V-Q) scan, 551
Vessel wall MRI (VW-MRI), 588
Video nailfold capillary microscopy (VNC), 69
Video-polysomnography (VPSG), 621, 624
Vincristine, 637, 703
Vitamin B12, 454, 709
Vitamin D, 391, 565
Vitamin K antagonists, 552
Vitiligo, 498, 707
  adaptive immunity, 496
  cosmetic modalities, 499
  diagnosis
    clinical manifestations, 497, 498
    pathology, 498
  epidemiology, 495
  genetic aspect, 496
  innate immunity, 496
  oxidative stress and intrinsic abnormalities in melanocytes and keratinocytes, 496
  pathogenesis, 496
  prognosis, 498
  treatment, 498
    emerging targeted therapies, 499
    phototherapy, 498, 499
    surgical, 499
    topical and systemic steroids, 499
    topical immunomodulators, 499
Vitritis, 639, 641
Vogt-Koyanagi-Harada Syndrome (VKH), 641, 643
  classical histopathological findings, 644
  clinical manifestations, 644
  complementary exams, 645
  cutaneous manifestations, 644
  diagnostic criteria, 645, 646
  differential diagnosis, 645
  early steroid therapy, 646
  etiology, 643
  extraocular manifestations, 644
  immunobiological agents, 647
  immunosuppressants, 646
  standard therapy for, 646
Voltage-gated calcium channel (VGCC) antibodies, 573
von Willebrand factor (vWF), 735, 747

W
Warm AIHA (wAIHA), 699, 701
Western blot (WB) analysis, 389, 599
White globe appearance (WGA), 455
Widespread musculoskeletal pain, 309, 312, 314
Widespread Pain Index (WPI), 311, 312, 314

X
Xanthomatous hypophysitis (X-H), 384

Z
Zika virus, 579